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NEWS 30	Oct 24	Nutraceuticals International (NUTRACEUT) now available on STN
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L5 ANSWER 1 OF 34 CAPLUS COPYRIGHT 2002 ACS
2002:521462 Document No. 137:88442 Incensole and furanogermacrens and compounds in treatment for inhibiting neoplastic lesions and microorganisms. Shanahan-Pendergast, Elisabeth (Ire.). PCT Int. Appl. WO 2002053138 A2 20020711, 68 pp. DESIGNATED STATES: W: AE, AG, AT, AU, BB, BG, CA, CH, CN, CO, CU, CZ, LU, LV, MA, MD, UA, UG, US, VN, YU, RU, TJ, TM; RW: AT, BE, CH, CY, DE, ES, FI, ML, MR, NE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2002-IE1 20020102. PRIORITY: IE 2001-2 20010102.
AB The invention discloses the use of incensole and/or furanogermacrens, derivs. metabolites and precursors thereof in the treatment of neoplasia,

particularly resistant neoplasia and immundysregulatory disorders. These compds. can be administered alone or in combination with conventional chemotherapeutic, antiviral, antiparasite agents, radiation and/or surgery. Incensole and furanogermacren and their mixt. showed antitumor activity against various human carcinomas and melanomas and antimicrobial activity against Staphylococcus aureus and Enterococcus faecalis.

L5 ANSWER 2 OF 34 CAPLUS COPYRIGHT 2002 ACS

2002:466051 Document No. 137:42094 Preparation of **fusion** proteins with enhanced in vivo activity containing erythropoietin fused to a **human chorionic gonadotropin .beta.** subunit fragment. Lee, Dong-Eok; Oh, Myung-Suk; Kim, Ki-Wan; Chung, Bo-Sup; Ha, Byung-Jhip; Park, Ji-Sook (Cheil Jedang Corporation, S. Korea). PCT Int. Appl. WO 2002048194 A1 20020620, 30 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-KR2137 20011210. PRIORITY: KR 2000-75230 20001211; KR 2001-72713 20011121.

AB The present invention relates to a **fusion** protein in which a carboxy terminal of human erythropoietin (EPO) is fused with a carboxy terminal peptide fragment of **.beta.** subunit of **human chorionic gonadotropin**(HCG), to DNA encoding the **fusion** protein, and to a method for prepn. of the **fusion** protein. The **fusion** protein has enhanced in vivo erythropoietin activity.

L5 ANSWER 3 OF 34 CAPLUS COPYRIGHT 2002 ACS

2002:52003 Document No. 136:117371 Method of inducing an immunological CTL response by lymphatic system delivery of peptide vaccine. Kundig, Thomas M.; Simard, John J. L. (Switz.). U.S. Pat. Appl. Publ. US 2002007173 A1 20020117, 48 pp., Cont.-in-part of U. S. Ser. No. 380,534. (English). CODEN: USXXCO. APPLICATION: US 2001-776232 20010202. PRIORITY: CA 1997-2209815 19970710; US 1997-988320 19971210; WO 1998-US14289 19980710; US 1999-380534 19990901.

AB Disclosed herein are methods for inducing an immunol. CTL response to an antigen by sustained, regular delivery of the antigen to a mammal so that the antigen reaches the lymphatic system. Antigen is delivered at a level sufficient to induce an immunol. CTL response in a mammal and the level of the antigen in the mammal's lymphatic system is maintained over time sufficient to maintain the immunol. CTL response. Also disclosed is an article of manuf. for delivering an antigen that induces a CTL response in an animal. The antigen can be used in vaccines for cancer or infection.

L5 ANSWER 4 OF 34 MEDLINE DUPLICATE 1

2002477314 Document Number: 22224481. PubMed ID: 12239121. Transgenic mice harboring murine luteinizing hormone receptor promoter/**beta** -galactosidase **fusion** genes: different structural and hormonal requirements of expression in the testis, ovary, and adrenal gland. Hamalainen Tuula; Kero Jukka; Poutanen Matti; Huhtaniemi Ilpo. (Department of Physiology, University of Turku, Finland.) ENDOCRINOLOGY, (2002 Oct) 143 (10) 4096-103. Journal code: 0375040. ISSN: 0013-7227. Pub. country: United States. Language: English.

AB In vivo regulation of the LH receptor (LHR) promoter was studied using transgenic (TG) mice harboring **fusion** genes containing three different lengths of the LHR promoter (7.4 kb, 2.1 kb, and 173 bp), fused with coding sequence of the Escherichia coli **beta**-galactosidase (**beta**-GAL) reporter gene. The length of the LHR promoter significantly affected the pattern of **beta**-GAL expression. In

the testis the shortest promoter directed expression primarily of the full-length **beta**-GAL mRNA, but mainly truncated messages were transcribed from the longer LHR promoter/**beta**-GAL constructs. The case was reversed in the ovary and adrenal gland. Furthermore, we have recently detected strong LHR expression in the adrenal gland of female mice with chronically elevated serum LH. Therefore, the regulation of the adrenal LHR expression was addressed in the present study using the LHR/**beta**-GAL TG mice. Elevated LH levels were achieved in the LHR/**beta**-GAL mice either by gonadectomy or cross-breeding them with TG mice overexpressing a **chimeric** protein of bovine LH **beta**-subunit and the C-terminal fragment of **human chorionic gonadotropin-beta**. In both models, **beta**-GAL mRNA was found in the adrenal cortex when the 7.4-kb LHR promoter was applied but not in mice carrying the 173-bp LHR promoter. The 7.4-kb construct was activated also in the ovaries in the double TG LHR(**beta**-GAL)/bovine LH **beta**-subunit/C-terminal fragment of **human chorionic gonadotropin**-betamice in some theca-interstitial cells surrounding the follicles. Hence, the LHR promoter elements essential for directing **beta**-GAL expression to the adrenal gland and ovary (7.4 kb) are different from those recently shown to be essential for the testicular expression (173 bp). In conclusion, elevated serum LH concentrations were found seminal for the LHR promoter activation in the ovaries and adrenals, and different lengths of the promoter are responsible for reporter gene expression in the testis, ovary, and adrenal gland.

L5 ANSWER 5 OF 34 CAPLUS COPYRIGHT 2002 ACS

2001:924101 Document No. 136:50663 Recombinant phycobiliprotein and phycobiliprotein linker **fusion** proteins and uses therefore. Allnutt, F. C. Thomas; Toole, Colleen M.; Morseman, John P. (Martek Biosciences Corporation, USA). PCT Int. Appl. WO 2001096871 A2 20011220, 34 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US19439 20010618. PRIORITY: US 2000-PV211784 20000616.

AB This invention is directed to the utilization of the developing methods for mol. manipulation of cyanobacteria and red algae (and potentially cryptomonad algae) to express of phycobiliproteins and phycobiliprotein linker **fusion** proteins and their utilization as phycobiliprotein, phycobilisome and subassembly based reagents. In particular, the present invention relates to a method for a specific binding assay to det. a target moiety which is a member of a specific binding pair, and provides an improvement in the method comprising using a detectable label which is a **fusion** protein contg. both a phycobiliprotein domain and another domain corresponding to a 1st member of a specific binding pair, where the **fusion** protein binds to a 2nd member of the specific binding pair to provide a detectable labeled complex. The domain derived from the 1st member of the specific binding pair can be directly fused to the phycobiliprotein or phycobiliprotein linker domain or be sepd. by a spacer that allows correct folding of both domains.

L5 ANSWER 6 OF 34 CAPLUS COPYRIGHT 2002 ACS

2001:145198 Document No. 134:188974 DNA encoding human hybrid heterodimeric proteins for modulation of protein-protein interactions. Campbell, Robert K.; Jameson, Bradford A.; Chappel, Scott C. (Applied Research Systems ARS Holding N.V., Neth. Antilles). U.S. US 6194177 B1 20010227, 35 pp., Cont.-in-part of U.S. Ser. No. 804,166. (English). CODEN: USXXAM.

APPLICATION: US 1997-910991 19970814. PRIORITY: US 1996-PV11936 19960220; US 1997-804166 19970220.

AB This invention relates to a hybrid protein of two amino acid sequences joined directly or with a peptide linker. Each hybrid protein sequence contains the binding portion of a receptor, such as tumor necrosis factor receptor 1 (TBP1), or a ligand linked to a subunit of a heterodimeric proteinaceous hormone, such as **human chorionic gonadotropin** (hCG). Each hybrid protein sequence contains a corresponding hormone subunit so as to form a heterodimer upon coexpression. Corresponding DNA mols., expression vectors, host cells, and a method of producing such proteins are claimed. These hybrid proteins could result in monofunctional, bifunctional, or multifunctional mols. for modulating protein-protein interactions, for example by sequestering ligands or regulating receptor activity. Recombinant **fusion** proteins TBP1-hCG(.alpha./.**beta**.) were produced, secreted into culture media of transfected mammalian cells, and formed heterodimers. The TBP1-hCG(.alpha./.**beta**.) proteins inhibited tumor necrosis factor cytotoxicity in a bioassay using the human breast carcinoma cell line BT-20. A plasmid was constructed for expression of the FSH .**beta**. subunit fused to the extracellular domain of the FSH receptor with a thrombin cleavage site and thrombin receptor extracellular tethering domain.

L5 ANSWER 7 OF 34 SCISEARCH COPYRIGHT 2002 ISI (R)

2001:405896 The Genuine Article (R) Number: 431KE. High-level bacterial expression of a natively folded, soluble extracellular domain **fusion** protein of the human luteinizing hormone/chorionic gonadotropin receptor in the cytoplasm of Escherichia coli. Lobel L I; Pollak S; Klein J; Lustbader J W (Reprint). Columbia Univ, Dept Obstet & Gynecol, Ctr Reprod Sci, 630 W 168th St, New York, NY 10032 USA (Reprint); Columbia Univ, Dept Obstet & Gynecol, Ctr Reprod Sci, New York, NY 10032 USA. ENDOCRINE (MAR 2001) Vol. 14, No. 2, pp. 205-212. Publisher: HUMANA PRESS INC. 999 RIVERVIEW DRIVE SUITE 208, TOTOWA, NJ 07512 USA. ISSN: 0969-711X. Pub. country: USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB We have expressed the extracellular domain of the human luteinizing hormone/chorionic gonadotropin (hLH/CG) receptor as a **fusion** protein with thioredoxin in the cytoplasm of an Escherichia coli strain that contains mutations in both the thioredoxin reductase and glutathione reductase genes. The **chimeric** protein isolated following induction of expression is purified in a soluble form and binds hCG with an affinity approximating that of native receptor. This truncated form of the receptor displays the same specificity as intact hLH/CG receptor and does not bind human follicle stimulating hormone. This cytoplasmically produced protein is expressed at levels that exceed 10 mg/L. Expression of properly folded extracellular domain of the hLH/CG receptor in the cytoplasm of E, coli allows the facile and economic purification of large quantities of material. This will facilitate the determination of the structure of the hormone-binding domain of the glycoprotein receptor as well as the production of epitope-specific antibodies.

L5 ANSWER 8 OF 34 CAPLUS COPYRIGHT 2002 ACS

2000:608604 Document No. 133:213048 Protein OmpA of Klebsiella pneumoniae associated with the **human chorionic gonadotropin** hormone or a compound involved in cell proliferation or fertility. Goetsch, Liliane; Corvaia, Nathalie; Beck, Alain; Haeuw, Jean-Francois; Bonnefoy, Jean-Yves (Pierre Fabre Medicament, Fr.). PCT Int. Appl. WO 2000050071 A1 20000831, 40 pp. DESIGNATED STATES: W: AU, BR, CA, CN, JP, MX, US, ZA; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (French). CODEN: PIXXD2. APPLICATION: WO 2000-FR463 20000224. PRIORITY: FR 1999-2314 19990224.

AB The invention concerns the use of a mixt. or complex comprising an enterobacterium membrane protein OmpA, in particular of Klebsiella

pneumoniae, assocd. with an immunogen selected among the .**beta**
.hCG, a compd. involved in tumor cell proliferation or fertility, or with one of their fragments, for prepg. a pharmaceutical compn. for enhancing the response against said immunogen. The invention further concerns a pharmaceutical compn. comprising said mixt. or complex in particular for preventing and for treating tumors, or for treating fertility.

L5 ANSWER 9 OF 34 CAPLUS COPYRIGHT 2002 ACS
2000:493402 Document No. 133:134164 Chorionic gonadotropin DNA vaccines and methods. Iversen, Patrick L. (Avi Biopharma, Inc., USA). PCT Int. Appl. WO 2000041717 A2 20000720, 45 pp. DESIGNATED STATES: W: AU, CA, JP, KR; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US30232 19991217. PRIORITY: US 1998-PV112910 19981218.
AB The invention relates to immunotherapy of a mammalian subject by exposing the immune response cells of the subject to a nucleic acid construct encoding at least one hCG immunogenic epitope or precursor thereof such that the nucleic acid construct is taken up and processed by the immune response cells. The invention further relates to compns. comprising such hCG-encoding nucleic acid constructs.

L5 ANSWER 10 OF 34 CAPLUS COPYRIGHT 2002 ACS
2000:420974 Document No. 133:38705 hCG therapy for the treatment of breast cancer. Russo, Irma H.; Russo, Jose; Deluca, Giampiero; Janssens, Jaak Ph (Fox Chase Cancer Center, USA; Applied Research Systems Ars Holdings N. V.). PCT Int. Appl. WO 2000035469 A2 20000622, 61 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US29795 19991215. PRIORITY: EP 1998-123817 19981215.
AB This invention relates to the field of cancer therapy. More particularly, the invention relates to the treatment of mammary tumor, clin. manifest mammary tumor (breast cancer) and metastatic mammary tumor by administration of **human Chorionic Gonadotropin** (hCG). The treatment preferably comprises the administration of hCG in conjunction with an antiestrogen and/or a Type I Interferon. A protein having the biol. activity of hCG and/or a binding activity toward the hCG receptor can be used in place of hCG. Pharmaceutical compns. contg. the compds. of the invention are also claimed as are articles of manuf. comprising the pharmaceutical compns.

L5 ANSWER 11 OF 34 CAPLUS COPYRIGHT 2002 ACS
2000:190950 Document No. 132:241954 **Human chorionic gonadotropin** vaccines. Harris, Jeffrey; Martinez, Mitzi (Zonagen, Inc., USA). PCT Int. Appl. WO 2000015253 A1 20000323, 39 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US21591 19990916. PRIORITY: US 1998-100766 19980917.
AB A method for the prodn. of the .**beta**.-subunit of **human chorionic gonadotropin** (.**beta**.hCG) proteins using recombinant technol., novel DNA sequences encoding such proteins, fragments, thereof, or analogs thereof, and the use of these recombinant proteins combined with adjuvant as a means of interrupting fertility in

mammals by the immunol. inactivation of the pregnancy hormone hCG.

L5 ANSWER 12 OF 34 CAPLUS COPYRIGHT 2002 ACS
2000:454238 Document No. 133:88233 Inhibitors of leaderless protein export. Florkiewicz, Robert Z.; Baird, Andrew (Ciblex Corporation, USA). U.S. US 6083706 A 20000704, 64 pp., Cont.-in-part of U.S. Ser. No. 807,014. (English). CODEN: USXXAM. APPLICATION: US 1998-30613 19980225. PRIORITY: US 1997-807014 19970226.
AB Methods of inhibiting the export of a leaderless protein from a cell by contacting the cell with a compd. that inhibits the binding of the leaderless protein and a transport mol. are provided. Leaderless proteins include FGF-1, FGF-2, IL-1.alpha., IL-1.**beta**., CNTF and HIV-tat; and the transport mol. is selected from a group of ion channels consisting of Ca+ATPase, H+/Na+ATPase, Na+ channel, Cl- channel and k+ channel. These methods are useful in treatment of various conditions, including angiogenesis, restenosis, tumors and diabetes.

L5 ANSWER 13 OF 34 MEDLINE
2000177750 Document Number: 20177750. PubMed ID: 10712435. Elevated luteinizing hormone induces expression of its receptor and promotes steroidogenesis in the adrenal cortex. Kero J; Poutanen M; Zhang F P; Rahman N; McNicol A M; Nilson J H; Keri R A; Huhtaniemi I T. (Department of Physiology, and. Department of Pediatrics, University of Turku, FIN-20520 Turku, Finland. Department of Pathology, Glasgow Royal Infirmary, Castle Street, Glasgow G4 0SF, United Kingdom.) JOURNAL OF CLINICAL INVESTIGATION, (2000 Mar) 105 (5) 633-41. Journal code: 7802877. ISSN: 0021-9738. Pub. country: United States. Language: English.
AB Transgenic (TG) female mice expressing bLHbeta-CTP (a **chimeric** protein derived from the **beta**-subunit of bovine luteinizing hormone [LH] and a fragment of the **beta**-subunit of **human chorionic gonadotropin** [hCG]) exhibit elevated serum LH, infertility, polycystic ovaries, and ovarian tumors. In humans, increased LH secretion also occurs in infertility and polycystic ovarian syndrome, often concomitant with adrenocortical dysfunction. We therefore investigated adrenal function in LH overexpressing bLHbeta-CTP female mice. The size of their adrenals was increased by 80% with histological signs of cortical stimulation. Furthermore, adrenal steroid production was increased, with up to 14-fold elevated serum corticosterone. Primary adrenal cells from TG and control females responded similarly to ACTH stimulation, but, surprisingly, the TG adrenals responded to hCG with significantly increased cAMP, progesterone, and corticosterone production. LH receptor (LHR) expression and activity were also elevated in adrenals from female TG mice, but gonadectomized TG females showed no increase in corticosterone, suggesting that the dysfunctional ovaries of the intact TG females promote adrenocortical hyperfunction. We suggest that, in intact TG females, enhanced ovarian estrogen synthesis causes increased secretion of prolactin (PRL), which elevates LHR expression. Chronically elevated serum LH, augmented by enhanced PRL production, induces functional LHR expression in mouse adrenal cortex, leading to elevated, LH-dependent, corticosterone production. Thus, besides polycystic ovaries, the bLHbeta-CTP mice provide a useful model for studying human disorders related to elevated LH secretion and adrenocortical hyperfunction.

L5 ANSWER 14 OF 34 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 2
2000:190055 Document No.: PREV200000190055. The immunogenicity of an engineered **chimeric** C-terminal peptide of **beta-human chorionic gonadotropin**. Wu Jianhua (1); Yan Jianhua; Yao Hong; et al. (1) Department of Gynecology and Obstetrics, Daping Hospital, Chongqing, 400042 China. Zhonghua Weishengwuxue He Mianyixue Zazhi, (March, 2000) Vol. 20, No. 2, pp. 110-115. ISSN: 0254-5101. Language: Chinese. Summary Language: Chinese; English.
AB Objective: To enhance the immunogenicity of the COOH-terminal peptide of

beta-human chorionic gonadotropin (betahCG-CTP) using molecular engineering. Methods: Based on the analysis of protein epitope and principles of immune recognition, a chimerical peptide comprised of the **beta** 8 and **beta** 9 epitopes of hCG and a "promiscuous" T cell epitope from the **fusion** protein of measles virus (MVF) was devised, synthesized and then purified. Rabbits were immunized with the chimerical peptide. The COOH-terminal peptide of **beta-human chorionic gonadotropin** coupled to diphtheria toxoid provided by WHO was served as control. Antibody titers were determined by enzyme-linked immunosorbent assay (ELISA). Results: The synthesized chimerical peptide elicited a much higher antibody response against intact native **human chorionic gonadotropin** than the control. Conclusion: The synthesized chimerical peptide is more immunogenic and there fore it is possible to enhance the immunogenicity of **beta** hCG-CTP via molecular engineering, which may be a promising approach for the making of an efficient vaccine for human fertility control.

L5 ANSWER 15 OF 34 CAPLUS COPYRIGHT 2002 ACS

2000:245148 Document No. 133:233272 Genetic Engineering of Single-Chain Gonadotropins and Hormone-Receptor **Fusion** Proteins. Narayan, Prema; Wu, Chengbin; Puett, David (Department of Biochemistry and Molecular Biology, University of Georgia, Athens, GA, 30602, USA). Methods (Orlando, Florida), 21(1), 59-66 (English) 2000. CODEN: MTHDE9. ISSN: 1046-2023. Publisher: Academic Press.

AB A review and discussion with 33 refs. The gonadotropin hormone family is distinguished by its heterodimeric structure in which the members share a common .alpha. subunit and a hormone-specific .**beta**. subunit. Since assembly of the heterodimer is often the rate-limiting step in prodn. of functional hormone, single-chain hormones have been engineered by genetically linking the two subunits. The single-chain hormone can in turn be fused to its receptor to produce a functional single-chain hormone-receptor complex. These **fusion** constructs offer a valuable new approach in structure-function studies and in the generation of hormone analogs. In this article we describe the exptl. design for the generation of single-chain **human chorionic gonadotropin** and single-chain hormone-receptor **fusion** complex and strategies for the expression of these **fusion** proteins. (c) 2000 Academic Press.

L5 ANSWER 16 OF 34 CAPLUS COPYRIGHT 2002 ACS

1999:673041 Document No. 131:282025 Improved methods for making hormone heterodimers for therapeutic and disagnostic purposes. Moyle, William R. (University of Medicine & Dentistry of New Jersey, USA). PCT Int. Appl. WO 9953065 A1 19991021, 73 pp. DESIGNATED STATES: W: AU, CA, JP; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US8018 19990413. PRIORITY: US 1998-59625 19980414.

AB The present invention relates to a method for prepg. heterodimeric analogs of cysteine knot proteins. More specifically, the invention relates to a method for forming a subunit combination of a cystein knot protein having an .alpha.-subunit and a .**beta**.-subunit to prep. a heterodimeric protein analog which comprises the steps of (a) attaching a dimerization domain to the amino termini of both an .alpha.-subunit and a .**beta**.-subunit of a cystein knot protein; and (b) dimerizing the .alpha.-subunit and a .**beta**.-subunit to form a heterodimeric protein analog. Dimerization domains were added to the following glycoprotein hormones: hCG and hLH and hFSH and hTSH and TGF.**beta**. and PDGF and NGF and Veg1 and bone morphogenic protein and activin and inhibin. Endopeptidase and furin cleavage sites were included to cleave the dimerization domain. Heterodimeric protein analogs prepd. include hCG/hFSH chimeras and hCG/hTSH chimeras, deglycosylated hormones, truncated and mutated glycoprotein hormones contg. hCG C-terminus. Addn.

of these domains is expected to enhance the half-lives of these hormone analogs, making them more therapeutically effective and clin. diagnostic. These increase circulation time and reduce the rate of hormone dissocn. Unlike single-chain proteins that are folded differently from the native hormones, hormone analogs that have two sep. subunits similar to those found naturally would be expected to have receptor binding and immunol. properties that are more similar to those of the parental mols.

L5 ANSWER 17 OF 34 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 3

2000:50431 Document No.: PREV200000050431. Deglycosylation of a bifunctional lutropin-follitropin agonist reduced its follitropin activity more than its lutropin activity. Trout, Susan W.; Han, Yi; Myers, Rebecca V.; Bernard, Michael P.; Moyle, William R. (1). (1) Department of Obstetrics and Gynecology, 675 Hoes Lane, Piscataway, NJ USA. Fertility and Sterility, (Dec., 1999) Vol. 72, No. 6, pp. 1093-1099. ISSN: 0015-0282. Language: English. Summary Language: English.

AB Objective: To design a drug that blocks the gonadal actions of lutropins and follitropins. Design: Controlled in vitro study. Setting: Academic laboratory. Patient(s): None. Intervention(s): We removed three glycosylation signals from an hCG-hFSH chimera known to have high affinity for LH and FSH receptors, expecting this would create a bifunctional antagonist (dgCFC). To offset the inhibition of subunit combination caused by deglycosylation of alpha-subunit loop 2, we prepared dgCFC as a single-chain **fusion** protein containing the alpha-subunit downstream of the **chimeric beta**-subunit. Main Outcome Measure(s): Receptor binding, cyclic adenosine monophosphate accumulation. Result(s): dgCFC bound LH or FSH receptors similar to hCG or hFSH. It was a partial agonist and had one tenth the efficacy of hFSH and two thirds the efficacy of hCG. Conclusion(s): The surprising high residual lutropin activity of dgCFC indicated that its FSH residues offset the effects of deglycosylation, suggesting this approach to preparing a bifunctional antagonist is unlikely to lead to a useful drug. The increased lutropin efficacy of dgCFC relative to deglycosylated hCG supports the idea that oligosaccharides modulate glycoprotein hormone efficacy through an influence on hormone conformation.

L5 ANSWER 18 OF 34 CAPLUS COPYRIGHT 2002 ACS

1999:417163 Document No. 131:209734 Biosynthesis of a single peptide chain containing **human chorionic gonadotropin** . **beta**. and C3D3 complement. Yu, Wei Kuan; Shen, Qing Xiang; Li, Da Jing; Zhou, Qing Ping; Shen, Wei Ying; Wang, Jian (Shanghai Institute of Cell Biology, Chinese Academy of Sciences, Shanghai, 200031, Peop. Rep. China). Shiyan Shengwu Xuebao, 32(1), 31-37 (Chinese) 1999. CODEN: SYSWAE. ISSN: 0001-5334. Publisher: Shanghai Kexue Jishu Chubanshe.

AB In view of the strong immunity-enhancing function of HEL-C3d3 complement designed by Dr. Paul W. Dempsey, we attempted to produce a similar recombinant protein of **human chorionic gonadotropin .beta**. (hCG.**beta**.). With polymerase chain reaction, we introduced a BamHI restriction site into the 3' terminal of hCG.**beta**. cDNA. Then we have it covalently attached to the C3d3 cDNA at the pre-designed BamHI/BglII site. Having the **chimeric** DNA correctly cloned into the protein nuclear polyhedrosis virus (AcNPV) expression vector pVL1393, we constructed the expression vector pVL1393-(hCG.**beta**.-C3d3). Through anti-hCG. **beta**. immunoaffinity chromatog., the recombinant hCG.**beta** .-C3d3 chimera polypeptide was purified from culture supernatant of insect cells infected by the recombinant viruses. In the RIA test, the expressed product competitively inhibits the binding of 125I-hCG.**beta**. to hCG.**beta**.-antibody. On SDS-PAGE and Western blot, the recombinant peptide hCG.**beta**.-C3d3 showed normal immunogenicity and a mol. wt. of 116 KD.

L5 ANSWER 19 OF 34 MEDLINE DUPLICATE 4
1998366576 Document Number: 98366576. PubMed ID: 9703016. Identification of novel transmembrane gene sequence and its use for cell-surface targeting of **beta** subunit of **human chorionic gonadotropin**. Gupta A; Chandrasekhar S; Pal R; Talwar G P; Singh O M. (National Institute of Immunology, New Delhi, India.) DNA AND CELL BIOLOGY, (1998 Jul) 17 (7) 573-81. Journal code: 9004522. ISSN: 1044-5498. Pub. country: United States. Language: English.

AB We identified a 685-nucleotide gene fragment that codes for the transmembrane and cytoplasmic domains of glycoprotein of the LEP strain rabies virus and carried out experiments designed to express a novel **fusion** protein on the cell surface. The cDNA encoding the membrane anchor sequence was fused in the correct reading frame to the 3' end of the cDNA encoding the **beta** subunit of **human chorionic gonadotropin** (**beta**(h)CG), a secretory glycoprotein that is used as an antigen for a contraceptive vaccine being developed in our laboratory. The **fusion** gene cassette was placed under the control of a vaccinia virus early promoter and cloned in a host-restricted fowlpox viral vector. The recombinants, when used to infect mammalian cells that do not allow the replication of fowlpox virus, expressed the N-terminal 135 amino acid residues of **beta**(h)CG anchored in the cell membrane by the 75-amino acid C-terminal sequence derived from rabies virus glycoprotein. This hybrid protein is correctly processed post-translationally and transported efficiently to the plasma membrane of non-permissive cells such that the anchored **beta**(h)CG molecule retains the correctly folded native antigenic epitope(s).

L5 ANSWER 20 OF 34 CAPLUS COPYRIGHT 2002 ACS
1998:42308 Document No. 128:111159 Treatment and prevention of cancer by administration of derivatives of **human chorionic gonadotropin**. Gallo, Robert C.; Bryant, Joseph; Lunardi-Iskandar, Yanto (University of Maryland Biotechnology Institute, USA; Gallo, Robert C.; Bryant, Joseph; Lunardi-Iskandar, Yanto). PCT Int. Appl. WO 9749432 A1 19971231, 158 pp. DESIGNATED STATES: W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, GH, HU, IL, IS, JP, KG, KP, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1997-US11210 19970624. PRIORITY: US 1996-669676 19960624; US 1996-709925 19960909.

AB The present invention relates to methods of treating or preventing cancer by administration of **human chorionic gonadotropin**, **.beta.-human chorionic gonadotropin**, a peptide contg. a sequence of a portion of **.beta.-human chorionic gonadotropin**, or a fraction of a source of **human chorionic gonadotropin** or **.beta.-human chorionic gonadotropin**. In a preferred embodiment, the invention provides methods of treating or preventing Kaposi's Sarcoma, breast cancer, lung cancer or prostate cancer. The invention further provides assays for the utility of particular **human chorionic gonadotropin** prepns. in the treatment or prevention of cancer. Pharmaceutical compns. and methods of administration are also provided.

L5 ANSWER 21 OF 34 CAPLUS COPYRIGHT 2002 ACS
1998:42294 Document No. 128:124125 Methods of promoting hematopoiesis using derivatives of **human chorionic gonadotropin**. Gallo, Robert C.; Bryant, Joseph; Lunardi-Iskandar, Yanto (University of Maryland Biotechnology Institute, USA; Gallo, Robert C.; Bryant, Joseph; Lunardi-Iskandar, Yanto). PCT Int. Appl. WO 9749418 A1 19971231, 175 pp. DESIGNATED STATES: W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ,

EE, GE, GH, HU, IL, IS, JP, KG, KP, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1997-US11209 19970624. PRIORITY: US 1996-669654 19960624; US 1996-709924 19960909.

AB The present invention relates to methods of treating or preventing diseases or disorders assocd. with hematopoietic deficiency by administration of **human chorionic gonadotropin**, **.beta.-human chorionic gonadotropin**, a peptide contg. a sequence of one or more portions of **.beta.-human chorionic gonadotropin**, or fractions of a source of native **human chorionic gonadotropin** or native **.beta.-human chorionic gonadotropin**. The invention also relates to methods of treating and preventing diseases or disorders assocd. with hematopoietic deficiency by administration of hematopoietic cells, the nos. of which have been increased by contacting the cells with a therapeutic of the invention. Pharmaceutical compns. and methods of administration are also provided.

L5 ANSWER 22 OF 34 CAPLUS COPYRIGHT 2002 ACS

1998:42256 Document No. 128:124124 Treatment and prevention of HIV infection by administration of derivatives of **human chorionic gonadotropin**. Gallo, Robert C.; Bryant, Joseph; Lunardi-Iskandar, Yanto (University of Maryland Biotechnology Institute, USA; Gallo, Robert C.; Bryant, Joseph; Lunardi-Iskandar, Yanto). PCT Int. Appl. WO 9749373 A2 19971231, 173 pp. DESIGNATED STATES: W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, GH, HU, IL, IS, JP, KG, KP, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1997-US11202 19970624. PRIORITY: US 1996-669681 19960624; US 1996-709948 19960909.

AB The present invention relates to **.beta.**-hCG, particularly certain **.beta.**-hCG peptides, and analogs and derivs. thereof. The invention also relates to fractions of a source of native hCG or native **.beta.**-hCG, which fractions are active in inhibiting HIV infection or replication, against Kaposi's sarcoma or have a pro-hematopoietic effect. The invention further relates to methods of treatment and prevention of HIV infection by administration of a therapeutic compd. of the invention. Such therapeutic compds. include hCG, **.beta.**-hCG and **.beta.**-hCG peptides, analogs and derivs. of hCG, **.beta.**-hCG and **.beta.**-hCG peptides, and nucleic acids encoding hCG, **.beta.**-hCG and **.beta.**-hCG peptides, and therapeutically and prophylactically effective fractions of sources of native hCG or native **.beta.**-hCG. Pharmaceutical compns. and methods of administration of therapeutics are also provided.

L5 ANSWER 23 OF 34 CAPLUS COPYRIGHT 2002 ACS

1997:568294 Document No. 127:244008 Recombinant **fusion** proteins comprising ligand-binding receptor fragment linked with hormone subunit, heterodimer formation, and pharmaceutical uses. Campbell, Robert K.; Jameson, Bradford A.; Chappel, Scott C. (Applied Research Systems ARS Holding N.V., Neth. Antilles; Campbell, Robert K.; Jameson, Bradford A.; Chappel, Scott C.). PCT Int. Appl. WO 9730161 A1 19970821, 60 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY,

KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1997-US2315 19970220. PRIORITY: US 1996-11936 19960220.

AB This invention comprises a hybrid protein including two coexpressed amino acid sequences which form a heterodimer. Each sequence contains the binding portion of a receptor, such as tumor necrosis factor binding protein TBP1 or TBP2, or a ligand, such as interleukin-6, interferon-. **beta**., or thrombopoietin (TPO), linked to a subunit of a heterodimeric proteinaceous hormone, such as **human chorionic gonadotropin**. Each coexpressed sequence contains a corresponding hormone subunit so as to form a heterodimer upon expression. Corresponding DNA mols., expression vectors and host cells are also disclosed as are pharmaceutical compns. and a method of producing such proteins. The general method is exemplified by TBP1(20-161) **fusion** products with **human chorionic gonadotropin** .alpha. subunit coexpression with TBP1(20-161) **fusion** products with **human chorionic gonadotropin .beta.** subunit. The hybrid proteins were coexpressed by COS-7 cells, formed heterodimers, and protected BT-20 cells against TNF.alpha.-induced cytotoxicity.

L5 ANSWER 24 OF 34 CAPLUS COPYRIGHT 2002 ACS

1997:567075 Document No. 127:243345 Human thyroid-stimulating hormone (hTSH) subunit gene **fusion** produces hTSH with increased stability and serum half-life and compensates for mutagenesis-induced defects in subunit association. Grossmann, Mathis; Wong, Rosemary; Szkudlinski, Mariusz W.; Weintraub, Bruce D. (Laboratory of Molecular Endocrinology, Department of Medicine, Medical Biotechnology Center, University of Maryland School of Medicine and the Institute of Human Virology, Baltimore, MD, 21201, USA). Journal of Biological Chemistry, 272(34), 21312-21316 (English) 1997. CODEN: JBCHA3. ISSN: 0021-9258. Publisher: American Society for Biochemistry and Molecular Biology.

AB The human TSH (hTSH) subunits .alpha. and **.beta.** are transcribed from different genes and assoc. noncovalently to form the bioactive hTSH heterodimer. Dimerization is rate-limiting for hTSH secretion, and dissocn. leads to hormone inactivation. Previous studies on **human chorionic gonadotropin** (hCG) and human FSH had shown that it was possible by subunit gene **fusion** to produce a bioactive, single chain hormone. However, neither the stability nor the clearance from the circulation of such fused glycoprotein hormones has been studied. We show here that genetic **fusion** of the hTSH .alpha.- and **.beta.**-subunits using the carboxyl-terminal peptide of the hCG **.beta.**-subunit as a linker created unimol. hTSH whose receptor binding and bioactivity were comparable to native hTSH. Interestingly, the fused hTSH had higher thermostability and a longer plasma half-life than either native or dimeric hTSH contg. the hCG . **beta.**-subunit-carboxyl-terminal peptide, suggesting that dimer dissocn. may contribute to glycoprotein hormone inactivation in vivo. In addn., we show for the first time that synthesis of hTSH as a single polypeptide chain could overcome certain mutagenesis-induced defects in hTSH secretion, therefore enabling functional studies of such mutants. Thus, in addn. to prolongation of plasma half-life, genetic **fusion** of hTSH subunits should be particularly relevant for the engineering of novel analogs where desirable features are offset by decreased dimer formation or stability. Such methods provide a general approach to expand the spectrum of novel recombinant glycoprotein hormones available for in vitro and in vivo study.

L5 ANSWER 25 OF 34 CAPLUS COPYRIGHT 2002 ACS

1997:313310 Document No. 126:288197 Structure-function studies and protein engineering of glycoprotein hormones (hCG\.**beta**.). Campbell, Robert Kirwan (Rutgers, State Univ., New Brunswick, NJ, USA). 289 pp.

Avail. Univ. Microfilms Int., Order No. DA9711023 From: Diss. Abstr. Int., B 1997, 57(11), 6745 (English) 1996.
AB Unavailable

L5 ANSWER 26 OF 34 CAPLUS COPYRIGHT 2002 ACS
1997:313307 Document No. 126:288196 Use of **human chorionic gonadotropin**/bovine luteinizing hormone **.beta.**-subunit chimeras to define an epitope and localize determinants for receptor binding (lutropin, follitropin, hCG). Cosowsky, Laurey N. (Rutgers, State Univ., New Brunswick, NJ, USA). 133 pp. Avail. Univ. Microfilms Int., Order No. DA9711034 From: Diss. Abstr. Int., B 1997, 57(11), 6748 (English) 1996.
AB Unavailable

L5 ANSWER 27 OF 34 CAPLUS COPYRIGHT 2002 ACS
1997:114903 Document No. 126:181477 Immunogenicity of a **fusion** protein linking the **beta** subunit carboxyl terminal peptide (CTP) of **human chorionic gonadotropin** to the B subunit of Escherichia coli heat-labile enterotoxin (LTB). Rock, Edwin P.; Reich, Karl A.; Lyu, Dennis M.; Hovi, Marianne; Hardy, Jonathan; Schoolnik, Gary K.; Stocker, Bruce A.D.; Stevens, Vernon (Department of Microbiology and Immunology, Stanford University School of Medicine, Stanford, CA, 94305-5402, USA). Vaccine, 14(16), 1560-1568 (English) 1996. CODEN: VACCDE. ISSN: 0264-410X. Publisher: Elsevier.
AB **Human chorionic gonadotropin** (hCG) is currently under investigation as an antigenic target in both anticancer and antifertility vaccines. Formulations studied to date show promise in clin. trials for both applications yet are expensive to produce and require frequent administration to maintain an effective antibody titer. The authors have engineered a **fusion** protein consisting of Escherichia coli heat-labile enterotoxin subunit B (LTB) genetically linked at its C-terminus via a 9-amino acid linker to the 37-amino acid C-terminal peptide (CTP) of the hCG **beta** chain. This LTB-CTP **fusion** protein is stably expressed in bacteria and forms pentamers of full-length protein subunits. Purified LTB-CTP protein induces hCG-specific antibodies in mice without addnl. adjuvants.

L5 ANSWER 28 OF 34 CAPLUS COPYRIGHT 2002 ACS
1996:494525 Document No. 125:186186 Growth hormone (GH) retardation of muscle damage due to immobilization in old rats. Possible intervention with a new long-acting recombinant GH. Fares, Fuad A.; Gruener, Nachman; Carmeli, Eli; Reznick, Abraham Z. (Dep. Biochem., Carmel Med. Cent., Haifa, Israel). Annals of the New York Academy of Sciences, 786(Pharmacological Intervention in Aging and Age-Associated Disorders), 430-443 (English) 1996. CODEN: ANYAA9. ISSN: 0077-8923. Publisher: New York Academy of Sciences.
AB Four wk immobilization of the right leg of aged rats (26 mo old) caused a 31 and 27% decrease of muscle mass of the plantaris and soleus muscles, resp. In animals treated with growth hormone (0.6 mg/kg), the decrease in muscle wt. was only 14.7 and 16.1%, resp. Biochem. studies of the level of acid phosphatase as a marker of muscle catabolism showed a significant increase of this enzyme in the immobilized muscles. GH treatment had a pos. effect in curtailing the increase due to immobilization. Studies on muscle protein oxidn. used as another measure of damage in immobilized animals showed a 400% increase in protein carbonyls in plantaris muscles. GH decreased this value significantly. The authors also described the construction of chimera prepd. by **fusion** of human growth hormone with the carboxy terminal peptide of the **human chorionic gonadotropin** which may have a greater biopotency that human GH and may have pos. effects on old tissues.

L5 ANSWER 29 OF 34 SCISEARCH COPYRIGHT 2002 ISI (R) DUPLICATE 5
96:302400 The Genuine Article (R) Number: UE579. THE EXPRESSION OF HCG

EPITOPE FUSED TO HEPATITIS-B VIRUS CORE ANTIGEN. LI G D (Reprint); WANG B; CHEN Z Y; WANG Y; GONG Y T. ACAD SINICA, SHANGHAI INST BIOCHEM, SHANGHAI 200031, PEOPLES R CHINA. ACTA BIOCHIMICA ET BIOPHYSICA SINICA (MAR 1996) Vol. 28, No. 2, pp. 177-186. ISSN: 0582-9879. Pub. country: PEOPLES REPUBLIC OF CHINA. Language: Japanese.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The DNA fragments encoding HCG-**beta**-37-CTP was amplified by PCR and fused to the core gene of HBV at the position of amino acid 1(N-terminal **fusion**, pCn-HCG), 154(C-terminal **fusion**, pCc-HCG), 75-83(internal **fusion**, pCm-HCG), and both 75-83 and 154(pC-HCG2) respectively. The fused genes were expressed in E. coli., and the antigenicity of both HBcAg and HCG as well as the expression level were analyzed. In addition, the **chimeric** particular characteristics of the proteins and their immunogenicity were identified. It revealed that the **fusion** proteins pCm-HCG and pCc-HCG were able to form particles, and that the **fusion** protein pCm-HCG could induce antibody of anti-HCG of high titers in mice, suggesting that the position at 75-83 amino acid residue should be a relatively promising **fusion** site for HCG.

L5 ANSWER 30 OF 34 CAPLUS COPYRIGHT 2002 ACS

1996:613852 Document No. 125:317743 Synthesis of genetically fused single chain analog of **human chorionic gonadotropin** : Implications for drug design and structure-function relationships. Boime, Irving; Sugahara, Tadashi; Pixley, Mary R.; Perlas, Emerald; Hsueh, Aaron J. W. (School Medicine, Washington University, St. Louis, MO, 63110, USA). International Congress Series, 1106(Ovary: Regulation, Dysfunction and Treatment), 43-50 (English) 1996. CODEN: EXMDA4. ISSN: 0531-5131. Publisher: Elsevier.

AB A **chimeric** gene was constructed which encoded a **fusion** protein where the C-terminus of the **human chorionic gonadotropin** (hCG) **.beta.** subunit was fused directly to the N-terminus of the .alpha. subunit. Expression of this **chimeric** gene in CHO cells produced a single polypeptide hCG mol. that was biol. active in vitro and in vivo. Thus, the .alpha. and hCG. **beta.** subunits encoded as a single chain can fold into an appropriate conformation and a noncovalent linkage of the .alpha. and . **beta.** subunits is not required for biol. activity.

L5 ANSWER 31 OF 34 CAPLUS COPYRIGHT 2002 ACS

1995:761346 Document No. 123:161008 Recombinant thyrotropin containing a . **beta.**-subunit chimera with the **human chorionic gonadotropin**-**.beta.** carboxy-terminus is biologically active, with a prolonged plasma half-life: role of carbohydrate in bioactivity and metabolic clearance. Joshi, Lata; Murata, Yoko; Wondisford, Fredric E.; Szkudlinski, Mariusz W.; Desai, Rajesh; Weintraub, Bruce D. (Molecular and Cellular Endocrinology Branch, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 20892, USA). Endocrinology, 136(9), 3839-48 (English) 1995. CODEN: ENDOAO. ISSN: 0013-7227. Publisher: Endocrine Society.

AB Recombinant TSH is now successfully being used in clin. studies of thyroid cancer. Because of its therapeutic potential, the authors have constructed a longer acting analog of TSH by fusing the carboxy-terminal extension peptide (CTEP) of hCG.**beta.** onto TSH.**beta.**.. When coexpressed either with .alpha.-subunit complementary DNA or .alpha. minigene in African green monkey (COS-7) and human embryonic kidney (293) cells, the chimera was fully bioactive in vitro and exhibited enhanced in vivo potency assocd. with a prolonged plasma half-life. The addn. of 25 amino acids with 4 O-linked oligosaccharide chains did not affect the assembly and secretion of **chimeric** TSH. Wild-type (WT) and **chimeric** TSH secreted by COS-7 and 293 cells displayed wide differences in their plasma half-lives, presumably due to the presence of terminal sialic acid and SO4 on their oligosaccharide chains, resp.

Chimeric and WT TSH secreted by both cell lines demonstrated similar bioactivity in cAMP prodn., with some differences in [3H]thymidine incorporation. **Chimeric** TSH appears to be more effective in COS-7 cells than in 293 cells, as judged by growth assay. COS-7-produced **chimeric** TSH showed the max. increase in half-life, indicating the importance of sialic acid in prolonging half-life and in vivo potency. Sulfation of both subunits, predominantly .**beta**. and to a lesser extent .alpha., appears to be responsible at least in part for the increased metabolic clearance of WT and **chimeric** TSH secreted by 293 cells. Apart from its therapeutic potential, **chimeric** TSH produced in various cell lines can be used as a tool to delineate the roles of sulfate and sialic acid in the in vivo clearance and, thereby, the in vivo bioactivity.

L5 ANSWER 32 OF 34 CAPLUS COPYRIGHT 2002 ACS

1993:261008 Document No. 118:261008 Hormone analogs with extended half-life. Boime, Irving (Washington University, USA). PCT Int. Appl. WO 9306844 A1 19930415, 22 pp. DESIGNATED STATES: W: AT, AU, BB, BG, BR, CA, CH, CS, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, PL, RO, RU, SD, SE; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NL, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1992-US8424 19921002. PRIORITY: US 1991-771262 19911004.

AB Peptide and protein pharmaceuticals with extended half-life are prepd. The modified peptides and proteins contain .gtoreq.2 tandem extensions at their C-terminus comprising the carboxy terminal portion (CTP) of **human chorionic gonadotropin** (HCG). These CTP units consist essentially of the amino acid sequence found at positions 112-118 to position 145 of the .**beta**. subunit of HCG. **Chimeric** genes encoding human FSH contg. CTP repeats of sequences of HCG .**beta**. subunit were constructed by manipulation of the cloned sequences. Thus, 10 IU of the human FSH contg. the .**beta**. subunit extended by two CTP units prepd. as above was injected into rats. The serum level of unmodified human FSH in rats declined from 0.5 to <0.05 IU/mL over 8 h after injection of 10IU, while human FSH .**beta**.(CTP)2 remained substantially unchanged over this period declining from 0.8 to 0.5IU/mL.

L5 ANSWER 33 OF 34 CAPLUS COPYRIGHT 2002 ACS

1992:208630 Document No. 116:208630 Analogs of glycoprotein hormones having altered immunological characteristics, efficacy and/or receptor specificity. Campbell, Robert K.; Moyle, William R. (University of Medicine and Dentistry of New Jersey, USA). PCT Int. Appl. WO 9116922 A1 19911114, 93 pp. DESIGNATED STATES: W: CA, JP, US; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1991-US3162 19910507. PRIORITY: US 1990-520703 19900508.

AB **Chimeric** chorionic gonadotropin (CG) heterodimeric polypeptides are provided which have different properties compared to native human CG (hCG). Certain heterodimeric polypeptides bind to LH (LH) and FSH receptors and stimulate steroidogenesis in testicular and ovarian cells. Other heterodimeric polypeptides bind to LH receptors but have lower efficacy than hCG in stimulation of steroidogenesis in testicular and ovarian cells. Prodn. of the **chimeric** analogs by recombinant techniques is described, and sequences of chimeras are included. The steroidogenesis potency of the analogs was strongly related to receptor binding activity. One analog had reduced efficacy, relative to hCG, for LH receptor-mediated cAMP accumulation; the analog also inhibited the ability of hCG to stimulate hCG-induced cAMP accumulation.

L5 ANSWER 34 OF 34 CAPLUS COPYRIGHT 2002 ACS

1992:1748 Document No. 116:1748 Human thyroid-stimulating hormone receptor cDNA cloning and use in monoclonal antibody preparation. Milgrom, Edwin; Misrahi, Micheline; Loosfelt, Hugues; Atger, Michel (Institut National de

la Sante et de la Recherche Medicale (INSERM), Fr.). PCT Int. Appl. WO 9110735 A2 19910725, 49 pp. DESIGNATED STATES: W: JP, US; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE. (French). CODEN: PIXXD2. APPLICATION: WO 1991-FR25 19910115. PRIORITY: FR 1990-397 19900115.

AB A cDNA encoding the receptor for human TSH is cloned and expressed. The protein is used for the prepn. of monoclonal and polyclonal antibodies for use in the treatment of thyroid disorders (no data). The cDNA was cloned from a human thyroid cDNA bank in .lambda.gt10 by screening with porcine luteotropin/**human chorionic gonadotropin** receptor cDNA. Candidate clones were sequenced and confirmed by induction of thyroid hormone binding in COS cells. Transcription of the gene was limited to the thyroid gland. Monoclonal antibodies were prepd. against peptides from the hormone manufd. as **fusion** proteins with . **beta**.-galactosidase or with human ubiquitin in recombinant Escherichia coli.

=> dup remove l3
PROCESSING COMPLETED FOR L3
L6 103 DUP REMOVE L3 (77 DUPLICATES REMOVED)

=> s l6 and galactosidase
L7 7 L6 AND GALACTOSIDASE

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PROCESSING COMPLETED FOR L7
L8 7 DUP REMOVE L7 (0 DUPLICATES REMOVED)

=> d l8 1-7 cbib abs

L8 ANSWER 1 OF 7 MEDLINE

2002477314 Document Number: 22224481. PubMed ID: 12239121. Transgenic mice harboring murine luteinizing hormone receptor promoter/**beta** -**galactosidase fusion** genes: different structural and hormonal requirements of expression in the testis, ovary, and adrenal gland. Hamalainen Tuula; Kero Jukka; Poutanen Matti; Huhtaniemi Ilpo. (Department of Physiology, University of Turku, Finland.) ENDOCRINOLOGY, (2002 Oct) 143 (10) 4096-103. Journal code: 0375040. ISSN: 0013-7227. Pub. country: United States. Language: English.

AB In vivo regulation of the LH receptor (LHR) promoter was studied using transgenic (TG) mice harboring **fusion** genes containing three different lengths of the LHR promoter (7.4 kb, 2.1 kb, and 173 bp), fused with coding sequence of the Escherichia coli **beta**-**galactosidase** (**beta**-GAL) reporter gene. The length of the LHR promoter significantly affected the pattern of **beta**-GAL expression. In the testis the shortest promoter directed expression primarily of the full-length **beta**-GAL mRNA, but mainly truncated messages were transcribed from the longer LHR promoter/**beta**-GAL constructs. The case was reversed in the ovary and adrenal gland. Furthermore, we have recently detected strong LHR expression in the adrenal gland of female mice with chronically elevated serum LH. Therefore, the regulation of the adrenal LHR expression was addressed in the present study using the LHR/**beta**-GAL TG mice. Elevated LH levels were achieved in the LHR/**beta**-GAL mice either by gonadectomy or cross-breeding them with TG mice overexpressing a chimeric protein of bovine LH **beta**-subunit and the C-terminal fragment of **human chorionic gonadotropin-beta**. In both models, **beta**-GAL mRNA was found in the adrenal cortex when the 7.4-kb LHR promoter was applied but not in mice carrying the 173-bp LHR promoter. The 7.4-kb construct was activated also in the ovaries in the double TG LHR(**beta**-GAL)/bovine LH **beta** -subunit/C-terminal fragment of **human chorionic gonadotropin**-betamice in some theca-interstitial cells surrounding

the follicles. Hence, the LHR promoter elements essential for directing **beta**-GAL expression to the adrenal gland and ovary (7.4 kb) are different from those recently shown to be essential for the testicular expression (173 bp). In conclusion, elevated serum LH concentrations were found seminal for the LHR promoter activation in the ovaries and adrenals, and different lengths of the promoter are responsible for reporter gene expression in the testis, ovary, and adrenal gland.

L8 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2002 ACS
2000:190950 Document No. 132:241954 **Human chorionic gonadotropin** vaccines. Harris, Jeffrey; Martinez, Mitzi (Zonagen, Inc., USA). PCT Int. Appl. WO 2000015253 A1 20000323, 39 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US21591 19990916. PRIORITY: US 1998-100766 19980917.
AB A method for the prodn. of the **.beta.**-subunit of **human chorionic gonadotropin** (**.beta.**hCG) proteins using recombinant technol., novel DNA sequences encoding such proteins, fragments, thereof, or analogs thereof, and the use of these recombinant proteins combined with adjuvant as a means of interrupting fertility in mammals by the immunol. inactivation of the pregnancy hormone hCG.

L8 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2002 ACS
1992:1748 Document No. 116:1748 Human thyroid-stimulating hormone receptor cDNA cloning and use in monoclonal antibody preparation. Milgrom, Edwin; Misrahi, Micheline; Loosfelt, Hugues; Atger, Michel (Institut National de la Sante et de la Recherche Medicale (INSERM), Fr.). PCT Int. Appl. WO 9110735 A2 19910725, 49 pp. DESIGNATED STATES: W: JP, US; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE. (French). CODEN: PIXXD2. APPLICATION: WO 1991-FR25 19910115. PRIORITY: FR 1990-397 19900115.
AB A cDNA encoding the receptor for human TSH is cloned and expressed. The protein is used for the prepn. of monoclonal and polyclonal antibodies for use in the treatment of thyroid disorders (no data). The cDNA was cloned from a human thyroid cDNA bank in .lambda.gt10 by screening with porcine luteotropin/**human chorionic gonadotropin** receptor cDNA. Candidate clones were sequenced and confirmed by induction of thyroid hormone binding in COS cells. Transcription of the gene was limited to the thyroid gland. Monoclonal antibodies were prepd. against peptides from the hormone manufd. as **fusion** proteins with . **beta.-galactosidase** or with human ubiquitin in recombinant Escherichia coli.

L8 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2002 ACS
1991:36148 Document No. 114:36148 Study on hCG antigen. Part III. Immunological and biological activity assay of **.beta.**-**galactosidase**-hCG containing hCG **.beta.**-subunit C-terminal peptide synthesized in .lambda.gt 11 hCG Y1089. Luo, Yuxiang; Liu, Jiesen; Liu, Xuegao; Wu, Boliang; Ye, Bin; Wang, Xuan (Cent. Reprod. Immunol. Res., Jinan Univ., Canton, Peop. Rep. China). Jinan Daxue Xuebao, Ziran Kexue Yu Yixueban, 11(1), 92-6 (Chinese) 1990. CODEN: JDXUET. ISSN: 1000-9965.
AB A **human chorionic gonadotropin** (hCG) . **beta.**-subunit C-terminal peptide-contg. hybrid protein, . **beta.-galactosidase**-hCG, produced by the recombinant .lambda.gt 11 hCG in host strain E. coli Y1089 was isolated and purified by ammonium sulfate pptn. and anti-**.beta.-galactosidase** affinity column. Pooled sera from various exptl. groups were tested for anti-**.beta.**-hCG activity in assays of in vivo neutralizing

activity, as detd. by the mouse uterine wt. assay. Sera from mice immunized with .**beta**.-**galactosidase**-hCG inhibited the in vivo hCG activity. Dild. 1/4 to 1/8, these sera completely inhibited the uterine wt. increase induced by the injection of hCG. Thus, the .**beta**.-**galactosidase**-hCG possess the antigenicity and biol. activity of the hCG .**beta**.-subunit C-terminal peptide. Double immunodiffusion tests showed that the antibody titer produced by mice against the .**beta**.-**galactosidase**-hCG was related to the injected amt. of .**beta**.-**galactosidase**-hCG, and the optimal immunized quantity was 18 .mu.g for a mouse.

L8 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2002 ACS
1990:116908 Document No. 112:116908 Immunogenicity of .**beta**.-**galactosidase**-hCG polymer containing hCG-.**beta**.-subunit C-terminal peptide synthesized in .lambda.gt11 hCG Y1089. Luo, Yuxiang; Liu, Jieshen; Wu, Boliang; Wu, Xiaying; Wang, Xuan (Cent. Reprod. Immunol. Res., Jinan Univ., Guangzhou, Peop. Rep. China). Jinan Daxue Xuebao, Ziran Kexue Yu Yixueban (1), 53-9 (Chinese) 1989. CODEN: JDXUET. ISSN: 1000-9965.

AB A hybrid protein composed of bacterial .**beta**.-**galactosidase** and **human chorionic gonadotropin** (hCG) was produced by recombinant Escherichia coli. The hybrid protein contained the C-terminal 36 amino acids of hCG. The hybrid protein polymd. naturally. The polymd. hybrid protein was depolymd. in a soln. contg. 2M urea, 0.4M SDS, and 0.005M mercaptoethanol, at 60.degree.. Antibodies from rabbits and mice immunized by the monomer hybrid protein were reactive against intact hCG. Antibodies to the polymd. hybrid protein did not react with hCG.

L8 ANSWER 6 OF 7 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
1989:135908 Document No.: BA87:70561. TRANSCRIPTIONAL INHIBITION BY A GLUCOCORTICOID RECEPTOR-**BETA-GALACTOSIDASE** **FUSION** PROTEIN. ORO A E; HOLLENBERG S M; EVANS R M. HOWARD HUGHES MED. INST., SALK INST. BIOL. STUDIES, LA JOLLA, CALIF. 92138.. CELL, (1988) 55 (6), 1109-1114. CODEN: CELLB5. ISSN: 0092-8674. Language: English.

AB Binary developmental decisions and homeostatic regulation by steroids require negative transcriptional regulation to balance steroid-mediated stimulatory effects. Human glucocorticoid receptor mutants were used to identify regions important for trans-repression of the gene encoding the .alpha. subunit of chorionic gonadotropin. While the amino terminus is not critical, the DNA binding and ligand binding domains are required for efficient repression. However, the function of the carboxyl terminus can be substituted by a polypeptide from the human mineralocorticoid receptor or .**beta**.-**galactosidase** gene. The function of these **fusion** repressors supports the model that the human glucocorticoid receptor negatively regulates transcription via a stearic hindrance mechanism. These results suggest a potentially general strategy for creation of sequence-specific transcriptional repressors.

L8 ANSWER 7 OF 7 MEDLINE
84113049 Document Number: 84113049. PubMed ID: 6663149. Monoclonal antibodies to **human chorionic gonadotropin** and its **beta**-subunit. Furuhashi Y; Mano H; Hattori S; Goto S; Tomoda Y. NIPPON SANKA FUJINKA GAKKAI ZASSHI. ACTA OBSTETRICA ET GYNAECOLOGICA JAPONICA, (1983 Dec) 35 (12) 2415-20. Journal code: 7505749. ISSN: 0300-9165. Pub. country: Japan. Language: English.

AB Using the technique of somatic cell **fusion**, monoclonal antibodies to **human chorionic gonadotropin** (hCG) and its **beta**-subunit were produced. Spleen cells from immunized mice were fused with the myeloma line NS-1 using 50% polyethylene glycol and cultured in a selection medium. A sensitive enzyme immunoassay was performed for antibody screening using immobilized

solid-phase antigen and anti-mouse IgG Fab' (rabbit)-**beta**-D-**galactosidase** complex. Three double-cloned hybridomas (named 4H10, 4G2 and 1D12) were obtained. Anti-hCG 4H10 antibody reacted with hCG, the alpha-subunit of hCG (alpha-hCG) and human luteinizing hormone (hLH); and anti-hCG 4G2 antibody reacted with hCG and the **beta**-subunit of hCG (**beta**-hCG). It was interesting that anti-**beta**-hCG 1D12 antibody had the capacity to bind with free **beta**-hCG but not with intact hCG, which suggests that the 1D12 antibody can recognize a determinant site that is unique to **beta**-hCG. This unique epitope in **beta**-hCG might be expressed in or near a part which is hidden in the intact hCG molecule which is composed of alpha- and **beta**-subunits.

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L9 0 L7 AND FLAG

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(FILE 'HOME' ENTERED AT 18:28:56 ON 20 NOV 2002)

FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 18:29:06 ON 20 NOV 2002
L1 54282 S HUMAN CHORIONIC GONADOTROPIN
L2 14681 S L1 AND BETA
L3 180 S L2 AND FUSION
L4 41 S L3 AND CHIMERIC
L5 34 DUP REMOVE L4 (7 DUPLICATES REMOVED)
L6 103 DUP REMOVE L3 (77 DUPLICATES REMOVED)
L7 7 S L6 AND GALACTOSIDASE
L8 7 DUP REMOVE L7 (0 DUPLICATES REMOVED)
L9 0 S L7 AND FLAG

=> s l6 and analog
L10 19 L6 AND ANALOG

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PROCESSING COMPLETED FOR L10
L11 19 DUP REMOVE L10 (0 DUPLICATES REMOVED)

=> d l11 1-19 cbib abs

L11 ANSWER 1 OF 19 CAPLUS COPYRIGHT 2002 ACS
2002:521462 Document No. 137:88442 Incensole and furanogermacrens and compounds in treatment for inhibiting neoplastic lesions and microorganisms. Shanahan-Pendergast, Elisabeth (Ire.). PCT Int. Appl. WO 2002053138 A2 20020711, 68 pp. DESIGNATED STATES: W: AE, AG, AT, AU, BB, BG, CA, CH, CN, CO, CU, CZ, LU, LV, MA, MD, UA, UG, US, VN, YU, RU, TJ, TM; RW: AT, BE, CH, CY, DE, ES, FI, ML, MR, NE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2002-IE1 20020102. PRIORITY: IE 2001-2 20010102.
AB The invention discloses the use of incensole and/or furanogermacrens, derivs. metabolites and precursors thereof in the treatment of neoplasia, particularly resistant neoplasia and immundysregulatory disorders. These compds. can be administered alone or in combination with conventional chemotherapeutic, antiviral, antiparasite agents, radiation and/or surgery. Incensole and furanogermacren and their mixt. showed antitumor activity against various human carcinomas and melanomas and antimicrobial activity against Staphylococcus aureus and Enterococcus faecalis.

L11 ANSWER 2 OF 19 CAPLUS COPYRIGHT 2002 ACS
2000:240985 Document No. 132:292701 Novel methods for therapeutic vaccination. Steinaa, Lucilla; Mouritsen, Soren; Nielsen, Klaus

Gregorious; Haaning, Jesper; Leach, Dana; Dalum, Iben; Gautam, Anand; Birk, Peter; Karlsson, Gunilla (M Amp E Biotech A/s, Den.). PCT Int. Appl. WO 2000020027 A2 20000413, 220 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-DK525 19991005. PRIORITY: DK 1998-1261 19981005; US 1998-PV105011 19981020.

AB A method is disclosed for inducing cell-mediated immunity against cellular antigens. More specifically, the invention provides for a method for inducing cytotoxic T-lymphocyte immunity against weak antigens, notably self-proteins. The method entails that antigen presenting cells are induced to present at least one CTL epitope of the weak antigen and at the same time presenting at least one foreign T-helper lymphocyte epitope. In a preferred embodiment, the antigen is a cancer specific antigen, e.g. prostate specific membrane antigen (PSM), Her2, or FGF8b. The method can be exercised by using traditional polypeptide vaccination, but also by using live attenuated vaccines or nucleic acid vaccination. The invention furthermore provides immunogenic **analogs** of PSM, Her2 and FGF8b, as well as nucleic acid mols. encoding these **analogs**. Also vectors and transformed cells are disclosed. The invention also provides for a method for identification of immunogenic **analogs** of weak or non-immunogenic antigens.

L11 ANSWER 3 OF 19 CAPLUS COPYRIGHT 2002 ACS

2000:190950 Document No. 132:241954 **Human chorionic gonadotropin** vaccines. Harris, Jeffrey; Martinez, Mitzi (Zonagen, Inc., USA). PCT Int. Appl. WO 2000015253 A1 20000323, 39 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US21591 19990916. PRIORITY: US 1998-100766 19980917.

AB A method for the prodn. of the .**beta**.-subunit of **human chorionic gonadotropin** (.**beta**.hCG) proteins using recombinant technol., novel DNA sequences encoding such proteins, fragments, thereof, or **analogs** thereof, and the use of these recombinant proteins combined with adjuvant as a means of interrupting fertility in mammals by the immunol. inactivation of the pregnancy hormone hCG.

L11 ANSWER 4 OF 19 CAPLUS COPYRIGHT 2002 ACS

2000:4734 Document No. 132:132467 A biologically active single chain **human chorionic gonadotropin analog** with altered receptor binding properties. Narayan, Prema; Gray, Judy; Puett, David (Department of Biochemistry and Molecular Biology, University of Georgia, Athens, GA, 30602-7229, USA). Endocrinology, 141(1), 67-71 (English) 2000. CODEN: ENDOAO. ISSN: 0013-7227. Publisher: Endocrine Society.

AB The hCG is a heterodimer consisting of an .alpha.-subunit common among all members of the glycoprotein hormone family, LH, FSH, and TSH, and a unique .**beta**.-subunit responsible for receptor specificity. Biol. active single chain **analogs** of these hormones have been engineered in which the C-terminus of the .**beta**.-subunit was fused to the N-terminus of the .alpha.-subunit (N-.**beta**.-.alpha.-C) either with or without a linker such as the hCG.**beta**

. C-terminal peptide (CTP). This tandem order of subunits was chosen based on studies suggesting that the N-terminal region of hCG.**beta**. and particularly the C-terminal region of the .alpha.-subunit are important in receptor binding and activation. Single chain hCG (YhCG1) can, in turn, be fused to the LH receptor to yield a hormone-receptor complex that is biol. active in transfected cells. Herein, the authors report the construction of a new single chain hCG **analog** (YhCG3) in which the C-terminus of the .alpha.-subunit is fused to the N-terminus of hCG.**beta**. via a CTP (N-.alpha.-CTP-.**beta**.-C). Compared with YhCG1, this **analog** binds receptor with a 25- to 30-fold lower affinity, but, surprisingly, is capable of stimulating intracellular cAMP levels to the same extent. Furthermore, YhCG3 can be covalently linked to its receptor to produce a biol. active complex that results in elevated levels of basal cAMP in transfected cells. These results suggest that free N- and C-termini of hCG.**beta**. and the .alpha.-subunit, resp., are not essential for receptor binding and activation and that YhCG3 is in a more efficacious conformation for receptor activation than YhCG1.

L11 ANSWER 5 OF 19 MEDLINE

2000230100 Document Number: 20230100. PubMed ID: 10764607. Genetic engineering of single-chain gonadotropins and hormone-receptor **fusion** proteins. Narayan P; Wu C; Puett D. (Department of Biochemistry and Molecular Biology, University of Georgia, Athens, Georgia 30602, USA.. narayan@bchiris.bmb.uga.edu) . METHODS, (2000 May) 21 (1) 59-66. Journal code: 9426302. ISSN: 1046-2023. Pub. country: United States. Language: English.

AB The gonadotropin hormone family is distinguished by its heterodimeric structure in which the members share a common alpha subunit and a hormone-specific **beta** subunit. Since assembly of the heterodimer is often the rate-limiting step in production of functional hormone, single-chain hormones have been engineered by genetically linking the two subunits. The single-chain hormone can in turn be fused to its receptor to produce a functional single-chain hormone-receptor complex. These **fusion** constructs offer a valuable new approach in structure-function studies and in the generation of hormone **analogs**. In this article we describe the experimental design for the generation of single-chain **human chorionic gonadotropin** and single-chain hormone-receptor **fusion** complex and strategies for the expression of these **fusion** proteins.

L11 ANSWER 6 OF 19 CAPLUS

1999:673041 Document No. 131:282025 Improved methods for making hormone heterodimers for therapeutic and disagnostic purposes. Moyle, William R. (University of Medicine & Dentistry of New Jersey, USA). PCT Int. Appl. WO 9953065 A1 19991021, 73 pp. DESIGNATED STATES: W: AU, CA, JP; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US8018 19990413. PRIORITY: US 1998-59625 19980414.

AB The present invention relates to a method for prepg. heterodimeric **analogs** of cysteine knot proteins. More specifically, the invention relates to a method for forming a subunit combination of a cystein knot protein having an .alpha.-subunit and a .**beta**.-subunit to prep. a heterodimeric protein **analog** which comprises the steps of (a) attaching a dimerization domain to the amino termini of both an .alpha.-subunit and a .**beta**.-subunit of a cystein knot protein; and (b) dimerizing the .alpha.-subunit and a .**beta**.-subunit to form a heterodimeric protein **analog**. Dimerization domains were added to the following glycoprotein hormones: hCG and hLH and hFSH and hTSH and TGF.**beta**. and PDGF and NGF and Vegl and bone morphogenic protein and activin and inhibin. Endopeptidase

and furin cleavage sites were included to cleave the dimerization domain. Heterodimeric protein **analogs** prepd. include hCG/hFSH chimeras and hCG/hTSH chimeras, deglycosylated hormones, truncated and mutated glycoprotein hormones contg. hCG C-terminus. Addn. of these domains is expected to enhance the half-lives of these hormone **analogs**, making them more therapeutically effective and clin. diagnostic. These increase circulation time and reduce the rate of hormone dissocn. Unlike single-chain proteins that are folded differently from the native hormones, hormone **analogs** that have two sep. subunits similar to those found naturally would be expected to have receptor binding and immunol. properties that are more similar to those of the parental mols.

L11 ANSWER 7 OF 19 CAPLUS COPYRIGHT 2002 ACS
1999:223048 Document No. 130:247459 Mutants of thyroid stimulating hormone subunits with improved bioactivity and stability. Weintraub, Bruce D.; Szkudlinski, Mariusz W. (University of Maryland, Baltimore, USA). PCT Int. Appl. WO 9915665 A2 19990401, 44 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-US19772 19980922. PRIORITY: US 1997-939472 19970922.

AB The present invention is based upon the discovery that mutant .alpha. subunits and mutant .**beta**. subunits each comprising amino acid substitutions relative to the wild type can be produced and assembled to form a mutant TSH heterodimer or TSH **analog** that possesses higher bioactivity in vitro and longer half life in vivo. A preferred mutant .alpha. subunit (to be used in conjunction with a modification to increase the serum half-life of the TSH heterodimer having the mutant .alpha. subunit) comprises four mutations: Q13K, E14K, P16K, and Q20K; a preferred mutant .**beta**. subunit comprises three mutations: I58R, E63R, and L69R. Multiple mutations within a subunit and modifications to increase the half-life of the TSH heterodimer (i.e., .**beta** .-subunit **fusion** with the C-terminal extension peptide of **human chorionic gonadotropin** and/or a . **beta**. subunit-.alpha. subunit **fusion**) can act synergistically to achieve bioactivity that is greater than the sum of the increase of the mutations and the long acting modifications. Accordingly, the present invention provides methods for using mutant TSH heterodimers, TSH **analogs**, fragments, and derivs. thereof for treating or preventing diseases of the thyroid, in particular thyroid cancer. The invention also relates to methods of diagnosis, prognosis and monitoring for thyroid-related functions. Pharmaceutical and diagnostic compns., methods of using mutant TSH heterodimers and TSH **analogs** with utility for treatment and prevention of metabolic and reproductive diseases are also provided.

L11 ANSWER 8 OF 19 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
2000:14717 Document No.: PREV200000014717. Genetic **fusion** of an alpha-subunit gene to the follicle-stimulating hormone and chorionic gonadotropin-**beta** subunit genes: Production of a bifunctional protein. Kanda, Masatoshi; Jablonka-Shariff, Albina; Sato, Asomi; Pixley, Mary R.; Bos, Ebo; Hiro'oka, Takashi; Ben-Menahem, David; Boime, Irving (1). (1) Department of Pharmacology, Washington University Medical School, 660 South Euclid, Saint Louis, MO, 63110 USA. Molecular Endocrinology, (Nov., 1999) Vol. 13, No. 11, pp. 1873-1881. ISSN: 0888-8809. Language: English. Summary Language: English.

AB The human glycoprotein hormones, hCG, TSH, LH, and FSH, are composed of a common alpha-subunit assembled to a hormone-specific **beta** -subunit. The subunits combine noncovalently early in the secretory

pathway and exist as heterodimers but not as multimers. LH/FSH are synthesized in the pituitary gonadotrophs, and several of the alpha-subunit sequences required for association with either the LHbeta or FSHbeta subunits are different. Thus, it is intriguing that no ternary complexes are observed for LH and FSH in vivo (e.g. two different **beta**-assembled to a single alpha-subunit). To examine whether the alpha-subunit can interact with more than one **beta**-subunit, and to study the conformational relationships between the ligand and the receptor, we constructed a vector encoding two tandemly arranged **beta**-subunits fused to a single alpha-subunit gene (FSHbeta-CGbeta-alpha). This approach permitted structure-function analyses of alpha/**beta** domain complexes without the possibility of subunit dissociation. We reported previously that the CGbeta or FSHbeta subunit gene can be genetically fused to the alpha-gene and the resulting single chains (CGbetaalpha and FSHbetaalpha, respectively) were biologically active. Here we demonstrate that a triple-domain single chain bearing the configuration FSHbeta-CGbeta-alpha is efficiently secreted from transfected Chinese hamster ovary (CHO) cells and exhibits high-affinity receptor binding to both FSH and LH/hCG receptors, comparable to the native heterodimers. These results indicate that the alpha-subunit can interact with each **beta**-subunit in the same complex and that an alpha-domain fused to a **beta**-domain can still interact with an additional **beta**-subunit. The data also demonstrate the remarkable flexibility of the receptor to accommodate the increased bulkiness of the triple-domain ligand. In addition, the formation of intrachain FSH- and CG-like complexes observed in a triple-domain single chain suggests that the alpha-subunit can resonate, i.e. shuttle between alpha-**beta** heterodimeric intermediates during the early stages of synthesis and accumulation in the endoplasmic reticulum. Such model compounds could be useful as substrates to generate a new class of **analogs** in which the ratio of the LH/FSH activity is varied. This could aid in the design of **analogs** that could be used to mimic the in vivo hormonal profiles.

L11 ANSWER 9 OF 19 SCISEARCH COPYRIGHT 2002 ISI (R)

1998:355789 The Genuine Article (R) Number: ZL530. Cyclic AMP-dependent protein kinases and human trophoblast cell differentiation in vitro. Keryer G (Reprint); Alsat E; Tasken K; EvainBrion D. UNIV PARIS 05, FAC SCI PHARMACEUT & BIOL PARIS, INSERM, U427, F-75270 PARIS 06, FRANCE (Reprint); UNIV OSLO, INST MED BIOCHEM, N-0317 OSLO, NORWAY. JOURNAL OF CELL SCIENCE (APR 1998) Vol. 111, Part 7, pp. 995-1004. Publisher: COMPANY OF BIOLOGISTS LTD. BIDDER BUILDING CAMBRIDGE COMMERCIAL PARK COWLEY RD, CAMBRIDGE, CAMBS, ENGLAND CB4 4DL. ISSN: 0021-9533. Pub. country: FRANCE; NORWAY. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Human trophoblast cells offer a unique in vitro model for the study of aspects of the dynamic processes occurring during cell **fusion** and syncytium formation. In the human placenta, mononuclear cytotrophoblasts aggregate and fuse to form a multinucleated syncytiotrophoblast. In vitro, the addition of cyclic AMP **analogs**, 8-bromo-cyclic-AMP or Sp-8-bromo-cyclic AMPS, promotes syncytiotrophoblast formation, as shown by the disappearance of immunostained E-cadherin and desmoplakin, and increased numbers of nuclei per syncytium. An antagonist of cyclic AMP, Rp-8-bromo-cyclic AMPS, and an inhibitor of the cyclic All IP-dependent protein kinase catalytic subunit, H-89, impair cell **fusion**, This led us to study the pattern of expression and subcellular localization of cyclic-AMP-dependent protein kinase subunits during syncytium formation. Cytotrophoblasts expressed the RI alpha and RII alpha regulatory subunits and the C alpha and C **beta** catalytic subunits, RI alpha was down-regulated during syncytium formation, No change in RII omega. protein levels was observed, but there was a drastic subcellular redistribution. RII alpha located in the Golgi-centrosomal area of cytotrophoblasts was scattered throughout

the cytoplasm of the syncytiotrophoblast. Interestingly, an accumulation of RII alpha was observed underneath the epical membrane of syncytiotrophoblast in vitro and in situ This suggests a key role of cyclic AMP-dependent protein kinase type II alpha during cell **fusion** and microvilli formation, both of which are essential for the secretory and transfer functions of the syncytiotrophoblast.

L11 ANSWER 10 OF 19 CAPLUS COPYRIGHT 2002 ACS

1998:42308 Document No. 128:111159 Treatment and prevention of cancer by administration of derivatives of **human chorionic gonadotropin**. Gallo, Robert C.; Bryant, Joseph; Lunardi-Iskandar, Yanto (University of Maryland Biotechnology Institute, USA; Gallo, Robert C.; Bryant, Joseph; Lunardi-Iskandar, Yanto). PCT Int. Appl. WO 9749432 A1 19971231, 158 pp. DESIGNATED STATES: W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, GH, HU, IL, IS, JP, KG, KP, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1997-US11210 19970624. PRIORITY: US 1996-669676 19960624; US 1996-709925 19960909.

AB The present invention relates to methods of treating or preventing cancer by administration of **human chorionic gonadotropin, .beta.-human chorionic gonadotropin,** a peptide contg. a sequence of a portion of . **beta.-human chorionic gonadotropin,** or a fraction of a source of **human chorionic gonadotropin** or **.beta.-human chorionic gonadotropin**. In a preferred embodiment, the invention provides methods of treating or preventing Kaposi's Sarcoma, breast cancer, lung cancer or prostate cancer. The invention further provides assays for the utility of particular **human chorionic gonadotropin** prepns. in the treatment or prevention of cancer. Pharmaceutical compns. and methods of administration are also provided.

L11 ANSWER 11 OF 19 CAPLUS COPYRIGHT 2002 ACS

1998:42294 Document No. 128:124125 Methods of promoting hematopoiesis using derivatives of **human chorionic gonadotropin**. Gallo, Robert C.; Bryant, Joseph; Lunardi-Iskandar, Yanto (University of Maryland Biotechnology Institute, USA; Gallo, Robert C.; Bryant, Joseph; Lunardi-Iskandar, Yanto). PCT Int. Appl. WO 9749418 A1 19971231, 175 pp. DESIGNATED STATES: W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, GH, HU, IL, IS, JP, KG, KP, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1997-US11209 19970624. PRIORITY: US 1996-669654 19960624; US 1996-709924 19960909.

AB The present invention relates to methods of treating or preventing diseases or disorders assocd. with hematopoietic deficiency by administration of **human chorionic gonadotropin , .beta.-human chorionic gonadotropin,** a peptide contg. a sequence of one or more portions of **.beta.-human chorionic gonadotropin,** or fractions of a source of native **human chorionic gonadotropin** or native **.beta.-human chorionic gonadotropin**. The invention also relates to methods of treating and preventing diseases or disorders assocd. with hematopoietic deficiency by administration of hematopoietic cells, the nos. of which have been increased by contacting the cells with a therapeutic of the invention. Pharmaceutical compns. and methods of administration are also provided.

L11 ANSWER 12 OF 19 CAPLUS COPYRIGHT 2002 ACS
1998:42256 Document No. 128:124124 Treatment and prevention of HIV infection by administration of derivatives of **human chorionic gonadotropin**. Gallo, Robert C.; Bryant, Joseph; Lunardi-Iskandar, Yanto (University of Maryland Biotechnology Institute, USA; Gallo, Robert C.; Bryant, Joseph; Lunardi-Iskandar, Yanto). PCT Int. Appl. WO 9749373 A2 19971231, 173 pp. DESIGNATED STATES: W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, GH, HU, IL, IS, JP, KG, KP, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1997-US11202 19970624. PRIORITY: US 1996-669681 19960624; US 1996-709948 19960909.

AB The present invention relates to **.beta.**-hCG, particularly certain **.beta.**-hCG peptides, and **analogs** and derivs. thereof. The invention also relates to fractions of a source of native hCG or native **.beta.**-hCG, which fractions are active in inhibiting HIV infection or replication, against Kaposi's sarcoma or have a pro-hematopoietic effect. The invention further relates to methods of treatment and prevention of HIV infection by administration of a therapeutic compd. of the invention. Such therapeutic compds. include hCG, **.beta.**-hCG and **.beta.**-hCG peptides, **analogs** and derivs. of hCG, **.beta.**-hCG and **.beta** .-hCG peptides, and nucleic acids encoding hCG, **.beta.**-hCG and . **beta.**-hCG peptides, and therapeutically and prophylactically effective fractions of sources of native hCG or native **.beta** .-hCG. Pharmaceutical compns. and methods of administration of therapeutics are also provided.

L11 ANSWER 13 OF 19 MEDLINE
97407919 Document Number: 97407919. PubMed ID: 9261143. Human thyroid-stimulating hormone (hTSH) subunit gene **fusion** produces hTSH with increased stability and serum half-life and compensates for mutagenesis-induced defects in subunit association. Grossmann M; Wong R; Szkudlinski M W; Weintraub B D. (Department of Medicine, University of Maryland School of Medicine and the Institute of Human Virology, Medical Biotechnology Center, Baltimore, Maryland 21201, USA.. grossman@umbi.umd.edu) . JOURNAL OF BIOLOGICAL CHEMISTRY, (1997 Aug 22) 272 (34) 21312-6. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB The human thyroid-stimulating hormone (hTSH) subunits alpha and **beta** are transcribed from different genes and associate noncovalently to form the bioactive hTSH heterodimer. Dimerization is rate-limiting for hTSH secretion, and dissociation leads to hormone inactivation. Previous studies on **human chorionic gonadotropin** (hCG) and human follicle-stimulating hormone had shown that it was possible by subunit gene **fusion** to produce a bioactive, single chain hormone. However, neither the stability nor the clearance from the circulation of such fused glycoprotein hormones has been studied. We show here that genetic **fusion** of the hTSH alpha- and **beta**-subunits using the carboxyl-terminal peptide of the hCG **beta**-subunit as a linker created unimolecular hTSH whose receptor binding and bioactivity were comparable to native hTSH. Interestingly, the fused hTSH had higher thermostability and a longer plasma half-life than either native or dimeric hTSH containing the hCG **beta**-subunit-carboxyl-terminal peptide, suggesting that dimer dissociation may contribute to glycoprotein hormone inactivation in vivo. In addition, we show for the first time that synthesis of hTSH as a single polypeptide chain could overcome certain mutagenesis-induced defects in hTSH secretion, therefore enabling functional studies of such mutants. Thus, in addition to prolongation of plasma half-life, genetic

fusion of hTSH subunits should be particularly relevant for the engineering of novel **analogs** where desirable features are offset by decreased dimer formation or stability. Such methods provide a general approach to expand the spectrum of novel recombinant glycoprotein hormones available for in vitro and in vivo study.

L11 ANSWER 14 OF 19 CAPLUS COPYRIGHT 2002 ACS

1996:613852 Document No. 125:317743 Synthesis of genetically fused single chain **analog** of **human chorionic gonadotropin**: Implications for drug design and structure-function relationships. Boime, Irving; Sugahara, Tadashi; Pixley, Mary R.; Perlas, Emerald; Hsueh, Aaron J. W. (School Medicine, Washington University, St. Louis, MO, 63110, USA). International Congress Series, 1106(Ovary: Regulation, Dysfunction and Treatment), 43-50 (English) 1996. CODEN: EXMDA4. ISSN: 0531-5131. Publisher: Elsevier.

AB A chimeric gene was constructed which encoded a **fusion** protein where the C-terminus of the **human chorionic gonadotropin** (hCG) .**beta**. subunit was fused directly to the N-terminus of the .alpha. subunit. Expression of this chimeric gene in CHO cells produced a single polypeptide hCG mol. that was biol. active in vitro and in vivo. Thus, the .alpha. and hCG.**beta**. subunits encoded as a single chain can fold into an appropriate conformation and a noncovalent linkage of the .alpha. and .**beta**. subunits is not required for biol. activity.

L11 ANSWER 15 OF 19 CAPLUS COPYRIGHT 2002 ACS

1995:682606 Document No. 123:75618 Erythropoietin **analogs** with additional glycosylation sites.. Elliot, Steven G.; Byrne, Thomas E. (Amgen Inc., USA). Eur. Pat. Appl. EP 640619 A1 19950301, 65 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE. (English). CODEN: EPXXDW. APPLICATION: EP 1994-112732 19940816. PRIORITY: US 1993-108016 19930817.

AB Erythropoietin (EPO) **analogs** having at least one addnl. site for glycosylation, or a rearrangement of at least one site for glycosylation are disclosed. The invention also relates to DNA sequences encoding said erythropoietin **analogs**, and recombinant plasmids and host cells for **analog** expression. Thus, 120 **analogs** were prepd. by std. oligonucleotide-directed mutagenesis procedures. The **analogs** included 48 different Asn substitution derivs. (for N-linked carbohydrate chains), 61 Ser/Thr substitution derivs. (for O-linked carbohydrate chains), 6 substitution derivs. having carbohydrate site rearrangements, and 3 derivs. C-terminally fused to the 28 C-terminal residues of **human chorionic gonadotropin**. Transfected DHFR- CHO cells with a functional .**beta**.-galactoside .alpha.2,6-sialyltransferase were also used to introduced addnl. 2,6-linked sialic acid residues. Recombinant isoforms contg. the wild-type amino acid sequence but differing levels of sialic acid content were isolated; there was a relationship between the relative in vivo specific activity of EPO and no. of sialic acid residues per EPO mol. from the isoforms 5 through 11 (activity was const. among isoforms 11-14). **Analogs** having one or more addnl. sites for carbohydrate chain attachment did not necessarily result in EPO mols. actually having addnl. carbohydrates chains. Two EPO **analogs** (Thr125EPO and Ser87Asn88Thr90EPO) having addnl. carbohydrate chains were purified and isoform mixts. having different sialic contents were isolated and studied in receptor binding assays, pharmacokinetic expts, and expts. to det. increase in hematocrit of mice. High sialic acid isoforms had a significantly longer in vivo half-life and promoted a greater increase in hematocrit than did isolated wild-type isoform 4 or recombinant human EPO, even though the **analog** high sialic acid isoforms did not bind as strongly to the receptor.

L11 ANSWER 16 OF 19 CAPLUS COPYRIGHT 2002 ACS

1995:761346 Document No. 123:161008 Recombinant thyrotropin containing a .**beta**.-subunit chimera with the **human chorionic gonadotropin**-.**beta**. carboxy-terminus is biologically active, with a prolonged plasma half-life: role of carbohydrate in bioactivity and metabolic clearance. Joshi, Lata; Murata, Yoko; Wondisford, Fredric E.; Szkudlinski, Mariusz W.; Desai, Rajesh; Weintraub, Bruce D. (Molecular and Cellular Endocrinology Branch, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 20892, USA). Endocrinology, 136(9), 3839-48 (English) 1995. CODEN: ENDOAO. ISSN: 0013-7227. Publisher: Endocrine Society.

AB Recombinant TSH is now successfully being used in clin. studies of thyroid cancer. Because of its therapeutic potential, the authors have constructed a longer acting **analog** of TSH by fusing the carboxy-terminal extension peptide (CTEP) of hCG.**beta**. onto TSH. **beta**.. When coexpressed either with .alpha.-subunit complementary DNA or .alpha. minigene in African green monkey (COS-7) and human embryonic kidney (293) cells, the chimera was fully bioactive in vitro and exhibited enhanced in vivo potency assocd. with a prolonged plasma half-life. The addn. of 25 amino acids with 4 O-linked oligosaccharide chains did not affect the assembly and secretion of chimeric TSH. Wild-type (WT) and chimeric TSH secreted by COS-7 and 293 cells displayed wide differences in their plasma half-lives, presumably due to the presence of terminal sialic acid and SO4 on their oligosaccharide chains, resp. Chimeric and WT TSH secreted by both cell lines demonstrated similar bioactivity in cAMP prodn., with some differences in [3H]thymidine incorporation. Chimeric TSH appears to be more effective in COS-7 cells than in 293 cells, as judged by growth assay. COS-7-produced chimeric TSH showed the max. increase in half-life, indicating the importance of sialic acid in prolonging half-life and in vivo potency. Sulfation of both subunits, predominantly .**beta**. and to a lesser extent .alpha., appears to be responsible at least in part for the increased metabolic clearance of WT and chimeric TSH secreted by 293 cells. Apart from its therapeutic potential, chimeric TSH produced in various cell lines can be used as a tool to delineate the roles of sulfate and sialic acid in the in vivo clearance and, thereby, the in vivo bioactivity.

L11 ANSWER 17 OF 19 CAPLUS COPYRIGHT 2002 ACS

1993:261008 Document No. 118:261008 Hormone **analogs** with extended half-life. Boime, Irving (Washington University, USA). PCT Int. Appl. WO 9306844 A1 19930415, 22 pp. DESIGNATED STATES: W: AT, AU, BB, BG, BR, CA, CH, CS, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, PL, RO, RU, SD, SE; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NL, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1992-US8424 19921002. PRIORITY: US 1991-771262 19911004.

AB Peptide and protein pharmaceuticals with extended half-life are prepd. The modified peptides and proteins contain .gtoreq.2 tandem extensions at their C-terminus comprising the carboxy terminal portion (CTP) of **human chorionic gonadotropin** (HCG). These CTP units consist essentially of the amino acid sequence found at positions 112-118 to position 145 of the .**beta**. subunit of HCG. Chimeric genes encoding human FSH contg. CTP repeats of sequences of HCG . **beta**. subunit were constructed by manipulation of the cloned sequences. Thus, 10 IU of the human FSH contg. the .**beta**. subunit extended by two CTP units prepd. as above was injected into rats. The serum level of unmodified human FSH in rats declined from 0.5 to <0.05 IU/mL over 8 h after injection of 10IU, while human FSH .**beta**. (CTP)2 remained substantially unchanged over this period declining from 0.8 to 0.5IU/mL.

L11 ANSWER 18 OF 19 CAPLUS COPYRIGHT 2002 ACS

1993:421212 Document No. 119:21212 **Analogs** of glycoprotein hormones having altered receptor binding specificity and activity and

methods for preparing and using same. Moyle, William R.; Campbell, Robert K. (University of Medicine and Dentistry of New Jersey, USA). PCT Int. Appl. WO 9222568 A1 19921223, 98 pp. DESIGNATED STATES: W: CA, JP, US; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1992-US5207 19920618. PRIORITY: US 1991-717151 19910618.

AB Heterodimeric polypeptides are disclosed which bind to vertebrate LH and FSH receptors with altered specificity and can be administered to provide a desired ratio of FSH:LH activity for infertility treatment. The polypeptides, produced by genetic engineering techniques, comprise an .alpha.-subunit from a glycoprotein hormone [e.g. **human chorionic gonadotropin** (hCG)] and a .**beta**.-subunit consisting of 4 subsequences homologous to: (a) residues 1-93 (hCG numbering) of the .**beta**.-subunit of hCG, LH, FSH, or TSH; (b) residues 94-97 (hCG numbering) of the .**beta**.-subunit of hCG or LH; (c) residues 98-100 (hCG numbering) of the .**beta**.-subunit of hCG, LH, FSH, or TSH; (d) residues 95-104 (FSH numbering) of the .**beta**.-subunit of FSH. The heterodimer has greater affinity for FSH receptors than does LH. Polypeptide variants that are hormonally inactive but cross-react immunol. can be used in diagnostic immunoassays, as immunogens, and in affinity purifn. of antibodies. Construction of plasmids encoding variant .**beta**.-subunits and their **analogs** and mutants is described, along with the effects of mutations on hormonal activity, receptor binding, and ability to combine with .alpha.-subunits.

L11 ANSWER 19 OF 19 CAPLUS COPYRIGHT 2002 ACS

1992:208630 Document No. 116:208630 **Analogs** of glycoprotein hormones having altered immunological characteristics, efficacy and/or receptor specificity. Campbell, Robert K.; Moyle, William R. (University of Medicine and Dentistry of New Jersey, USA). PCT Int. Appl. WO 9116922 A1 19911114, 93 pp. DESIGNATED STATES: W: CA, JP, US; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1991-US3162 19910507. PRIORITY: US 1990-520703 19900508.

AB Chimeric chorionic gonadotropin (CG) heterodimeric polypeptides are provided which have different properties compared to native human CG (hCG). Certain heterodimeric polypeptides bind to LH (LH) and FSH receptors and stimulate steroidogenesis in testicular and ovarian cells. Other heterodimeric polypeptides bind to LH receptors but have lower efficacy than hCG in stimulation of steroidogenesis in testicular and ovarian cells. Prodn. of the chimeric **analogs** by recombinant techniques is described, and sequences of chimeras are included. The steroidogenesis potency of the **analogs** was strongly related to receptor binding activity. One **analog** had reduced efficacy, relative to hCG, for LH receptor-mediated cAMP accumulation; the **analog** also inhibited the ability of hCG to stimulate hCG-induced cAMP accumulation.

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For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> s l13 and gonadotropin
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L14 1 L13 AND GONADOTROPIN

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L14 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS
2000:190950 Document No. 132:241954 Human chorionic **gonadotropin** vaccines. **Harris, Jeffrey**; Martinez, Mitzi (Zonagen, Inc., USA). PCT Int. Appl. WO 2000015253 A1 20000323, 39 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US21591 19990916. PRIORITY: US 1998-100766 19980917.
AB A method for the prodn. of the .beta.-subunit of human chorionic **gonadotropin** (.beta.hCG) proteins using recombinant technol., novel DNA sequences encoding such proteins, fragments, thereof, or analogs thereof, and the use of these recombinant proteins combined with adjuvant as a means of interrupting fertility in mammals by the immunol. inactivation of the pregnancy hormone hCG.

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L17 10 DUP REMOVE L16 (0 DUPLICATES REMOVED)

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L17 ANSWER 1 OF 10 CAPLUS COPYRIGHT 2002 ACS
2000:190950 Document No. 132:241954 Human chorionic **gonadotropin** vaccines. **Harris, Jeffrey**; Martinez, Mitzi (Zonagen, Inc., USA). PCT Int. Appl. WO 2000015253 A1 20000323, 39 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US21591 19990916. PRIORITY: US 1998-100766 19980917.
AB A method for the prodn. of the .beta.-subunit of human chorionic **gonadotropin** (.beta.hCG) proteins using recombinant technol., novel DNA sequences encoding such proteins, fragments, thereof, or analogs thereof, and the use of these recombinant proteins combined with adjuvant as a means of interrupting fertility in mammals by the immunol. inactivation of the pregnancy hormone hCG.

L17 ANSWER 2 OF 10 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
1994:460984 Document No.: PREV199497473984. The effect of site of injection of **gonadotropin**-releasing hormone (GnRH) and double insemination on repeat breeders. Graves, W. M.; **Montgomery, M. J.**. Univ. Tenn., Knoxville, TN USA. Journal of Dairy Science, (1994) Vol. 77, No. SUPPL. 1, pp. 64. Meeting Info.: Combined Meeting of the American Dairy Science Association and the American Society of Animal Science Minneapolis, Minnesota, USA July 11-15, 1994 ISSN: 0022-0302. Language: English.

L17 ANSWER 3 OF 10 CAPLUS COPYRIGHT 2002 ACS
1983:173549 Document No. 98:173549 Seasonal changes in serum levels of FSH, LH and testosterone and in semen parameters in stallions. **Harris, Joyce M.**; Irvine, Clifford H. G.; Evans, Margaret J. (Dep. Vet. Sci., Lincoln Coll., Canterbury, N. Z.). Theriogenology, 19(3), 311-22 (English) 1983. CODEN: THGNBO. ISSN: 0093-691X.

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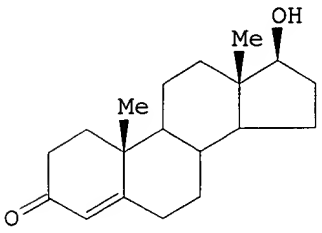

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AB In stallions in a temperate, insular climate, FSH [9002-68-0] concns. in serum were low in June (winter), began rising in July to peak in Sept., and remained significantly elevated through the end of Oct. and again in Dec., thereafter decreasing. Serum LH [9002-67-9] concns. began to increase in August and were significantly higher during Oct. through Dec. than in June and July. Although both FSH and LH increased during spring, FSH began to rise earlier and peaked 8 wk before LH. Seasonal changes in testosterone (I) [58-22-0] were similar to those in FSH, except peak concns. occurred .apprx.4 wk later. Vol. of gel-free semen, gel, spermatozoa per ejaculate, and libido all increased during the spring and summer months. Such seasonal changes may be an important consideration in stallion management.

L17 ANSWER 4 OF 10 MEDLINE
82275308 Document Number: 82275308. PubMed ID: 7051039. Disappearance of a urinary antigonadotrophin following HCG administration in Prader Willi syndrome. **Harris J C**; Knigge K M. PROGRESS IN CLINICAL AND BIOLOGICAL RESEARCH, (1982) 92 273-82. Journal code: 7605701. ISSN: 0361-7742. Pub. country: United States. Language: English.

L17 ANSWER 5 OF 10 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
1983:39481 Document No.: BR24:39481. DISAPPEARANCE OF A URINARY ANTI **GONADOTROPIN** FOLLOWING HUMAN CHORIONIC **GONADOTROPIN** ADMINISTRATION IN PRADER WILLI SYNDROME. **HARRIS J C**; KNIGGE K M. DIV. CHILD PSYCHIATRY, JOHN F. KENNEDY INST., JOHN HOPKINS HOSP., BALTIMORE, MD.. REITER, R. J. (ED.). PROGRESS IN CLINICAL AND BIOLOGICAL RESEARCH, VOL. 92. THE PINEAL AND ITS HORMONES; PROCEEDINGS OF AN INTERNATIONAL SYMPOSIUM, JAN. 2-9, 1982. XV+295P. ALAN R. LISS, INC.: NEW YORK, N.Y., USA. ILLUS. (1982) 0 (0), P273-282. CODEN: PCBRD2. ISSN: 0361-7742. ISBN: 0-8451-0092-0. Language: English.

L17 ANSWER 6 OF 10 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
82211526 EMBASE Document No.: 1982211526. Pre-pregnancy counselling of premalignant and malignant disease. **Harris J.W.**. United Kingdom. Clinics in Obstetrics and Gynaecology 9/1 (171-198) 1982. CODEN: COBGBA. Pub. Country: United Kingdom. Language: English.
AB This article reviews premalignant and malignant tumours of the pelvis, plus certain of the more common extrapelvic malignancies which, having been previously treated, now may be exposed to the influences of pregnancy. There is no doubt that the maxim, pregnancy should never be permitted in patients with premalignant and malignant disease is outmoded as a result of increased knowledge and management of the particular

disease. However, from what has been discussed above, it is obvious that a detailed knowledge of each condition and the prognosis for mother and fetus is essential if patients with these conditions are to be properly advised. It is particularly important that this advice should be given before a pregnancy occurs if a satisfactory outcome is to be achieved.

L17 ANSWER 7 OF 10 CAPLUS COPYRIGHT 2002 ACS
1979:18768 Document No. 90:18768 Immunological test reagent. Reckel, Rudolph; **Harris, Joanne** (Ortho Diagnostics, Inc., USA). Ger. Offen. DE 2812845 19780928, 16 pp. (German). CODEN: GWXXBX. APPLICATION: DE 1978-2812845 19780323.

AB A polymer of the general formula latex-(C(:O)NHR'N:CHR2CH = N)-X is prepd., where R' = C1-10 branched or unbranched alkyl- or dialkylamine, R2 = C1-10 alkyl, and X = antigen or antibody. The polymer is water insol. and can be used in serol. or immunoassay procedures. Thus, a carboxylated styrene-butadiene copolymer was combined with 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide-HCl and 3,3'-diaminodipropylamine, and after washing, the polymer was combined with human chorionic **gonadotropin** and glutardialdehyde. The final product could be used in a pregnancy test involving immunoassay.

L17 ANSWER 8 OF 10 CAPLUS COPYRIGHT 2002 ACS
1979:199881 Document No. 90:199881 Reagent for immunological test. Reckel, Rudolph; **Harris, Joanne** (Ortho Diagnostics, Inc., USA). Braz. Pedido PI BR 7801779 19781219, 26 pp. (Portuguese). CODEN: BPXXDX. APPLICATION: BR 1978-1779 19780322.

AB Reagents are prepd. for immunol. tests by the reaction of latex particles (0.05-1 .mu.m diam.) having a free CO2H group with a diamine in the presence of a carbodiimide as a condensing agent; the product is an amide having primary or secondary NH2 groups. The product then is reacted with an antigen or antibody, modified as necessary to contain NH2 groups, in the presence of bifunctional aldehyde, which results in condensation of the immunol. reagent with the NH2 groups of the modified latex by means of an aldehyde intermediary that acts as a bridge. In an example, PSI 83 (carboxylated polystyrene-butadiene particles contg. 20% butadiene) was reacted with 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide-HCl and (3,3'-diamino)dipropylamine. This product (3 vols. of 4% soln.) was then reacted with 2 vols. human chorionic **gonadotropin** (0.75 mg/mL) and 1 vol. of glutaraldehyde (0.25%). The product from this reaction can be used as an antigen in immunochem. tests. This technique has the advantage that the immunochem. reaction product is visible to the eye.

L17 ANSWER 9 OF 10 MEDLINE
65017722 Document Number: 65017722. OBESITY: A PROBLEM WITH MANY FACETS: OBSERVATIONS ON TREATMENT WITH CHORIONIC **GONADOTROPIN** AS AN ADJUNCT TO DIETARY MEASURES. **HARRIS J M;** WARSAW E. JOURNAL OF THE AMERICAN GERIATRICS SOCIETY, (1964 OCT) 12 987-95. ISSN: 0002-8614. Pub. country: United States. Language: English.

L17 ANSWER 10 OF 10 CAPLUS COPYRIGHT 2002 ACS
1954:39352 Document No. 48:39352 Original Reference No. 48:7075h-i,7076a-b Isolation and properties of .alpha.-corticotropin from sheep pituitary glands. Li, Choh Hao; Geschwind, Irving I.; Levy, Anthony L.; **Harris, J. Ieuan;** Dixon, Jonathan S.; Pon, Ning G.; Porath, Jerker O. (Univ. of California, Berkeley). Nature, 173, 251-3 (Unavailable) 1954.

AB cf. C.A. 46, 5180e; 47, 6023i. A peptide, possessing adrenal-stimulating activity, was isolated without pepsin digestion from a highly purified adrenocorticotropic hormone fraction (E) prepd. from sheep pituitary glands (C.A. 47, 6477b). Inactive material in fraction E was pptd. in 50% dioxane at pH 9.3-9.4. The supernatant was further purified by zone electrophoresis and the active peak obtained was chromatographed on an ion-exchange column (Amberlite XE-97). The active fraction was eluted

from the column and submitted to countercurrent distribution in 2-butanol/0.5% Cl3CCO2H followed by redistribution in 2-butanol/0.1% Cl3CCO2H. The peptide behaved as a single substance in countercurrent distribution, zone electrophoresis, chromatography, and carboxyl end-group analysis. Bioassay showed no significant contamination with thyratropin, somatotropin, **gonadotropin**, prolactin, or intermedin. The adrenal ascorbic acid-depleting activity was 150 international units per mg. Amino acid analyses of different prepns. did not indicate inhomogeneity. The molar ratios of amino acids were: alanine 3, arginine 3, aspartic acid 2, glutamic acid 5, glycine 3, histidine 1, leucine 1, lysine 4, methionine 1, phenylalanine 3, proline 4, serine 3, tryptophan 1, tyrosine 2, and valine 3. The min. mol. wt. was 4500 and the isoelec. point 7.0. Treatment with carboxypeptidase suggested that only one peptide chain exists in the hormone, ending in the C-terminal sequence leucine-glutamic acid-phenylalanine.

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---Logging off of STN---

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Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	181.47	181.68

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-30.98	-30.98

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